samples, and with a high prevalence of bronchiectasis–the latter proving to be a major predictor of CBI. These factors may limit the generalizability of the results and call for them to be validated. Lastly, the definition of CBI was not based on a single baseline assessment but on repeated sampling over time, which complicates its clinical utility as a risk prediction tool and may have confounded the observed relationship between CBI and pneumonia.

The results of this study are biologically plausible and logically appealing. The presence of low blood eosinophil counts and/or CBI appear to be risk factors that increase pneumonia risk and, therefore, influence the benefit–risk calculation for the use of ICS in COPD. That said, large-scale, routine, and repeated sputum collection and analysis poses logistic and implementation challenges, particularly in primary care. Unless this practical hurdle is overcome, it seems likely that decisions about ICS use will remain part science, part art. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Airway Occlusion Pressure Revisited

The use of airway occlusion pressure ($P_{0.1}$) as a measure of respiratory drive was introduced by Whitelaw and colleagues 45 years ago based on two basic assumptions (1). First, in the absence of flow or volume change during the occlusion, pressure generated by the inspiratory muscles is transmitted directly (1:1 ratio) to the external airway. Second, if the occlusion is brief (i.e., 0.1 s), there is no time for behavioral responses to influence the pressure output of the inspiratory muscles. Hence, the change in airway pressure during a constant brief time reflects the rate of rise of inspiratory muscle pressure at the beginning of spontaneous inspiration, which has been shown to correlate well with the rate of rise of inspiratory muscle activity, at least in normal subjects.

Originally Published in Press as DOI: 10.1164/rccm.202003-0585ED on March 23, 2020

Although the second tenet still holds true, several factors were subsequently identified that can alter the relation between P0.1 and inspiratory muscle pressure or electrical diaphragm muscle output in the absence of volume changes or behavioral responses. As noted by Whitelaw and Derenne in 1993, these factors include the presence of dynamic hyperinflation, expiratory muscle activity, chest wall distortion, respiratory muscle weakness, neuromuscular junction blockade, and the shape of the inspiratory pressure waveform (2). All of these modifiers apply to critically ill patients. In addition, the method used to measure P0.1 in such patients is of critical importance depending on whether a true occlusion is implemented, whether measurements are made close to the patient or remotely in the ventilator, what type of triggering is used, and other technical factors. Almost certainly, because of the numerous variables that modify the relation between P0.1 and inspiratory muscle pressure output or drive, the results of P0.1 in weaning assessments, even when measured properly with specialized equipment, have been variable and generally not impressive. There is, however, evidence that an excessively high or excessively low respiratory drive in patients is an important risk factor for continued ventilator dependence (3, 4). Identifying such patients would be of clinical value because this might spare them from being subjected to unsuccessful weaning trials and point to the abnormality that needs to be addressed.

The use of specialized equipment to measure P0.1 in the ICU is a major deterrent to such studies because the setup, proper application of occlusion, and assessment of the quality of the results require considerable expertise. Several commercially available ventilators measure P0.1 and display the results on the ventilator screen. The methods used by these ventilators vary but do not include the desirable application of occlusion near the patient's airway, and some ventilators do not even apply a true occlusion. An important practical question, therefore, is whether the ventilator-generated P0.1 is an adequate surrogate for the more complex and demanding use of specialized equipment.

In a study presented in this issue of the *Journal*, Telias and colleagues (pp. 1086–1098) compared P0.1 estimated by different commercial ventilators (P0.1*vent*) with values obtained in the proper way (P0.1*ref*) in critically ill patients and in a bench test using a simulator (5). In addition, they determined the relation between P0.1 and the pressure–time product of the inspiratory muscles. Not surprisingly, there were good correlations between P0.1 and pressure output in individual patients, consistent with the fact that airway pressure is directly related to respiratory muscle output during occluded breaths. Also, as expected from the various known modifiers of the relationship between P0.1 and inspiratory muscle pressure, there was much scatter in this relationship among patients. There are several important novel findings from this study. First, P0.1 measured by ventilators that apply a true end-expiratory occlusion accurately reflects P0.1*ref* in bench testing, whereas ventilators that do not apply occlusion are inaccurate. Second, on average, P0.1 measured by the more accurate ventilators in patients has little systematic error (minimal bias), and therefore these average values can be used to evaluate the impact of P0.1 on outcomes in group comparisons. Third, having defined a high respiratory output as P0.1 > 4.0 cm H_2O and a low output as <1.1 cm H_2O measured by P0.1*ref*, and notwithstanding the large differences between P0.1*vent* and P0.1*ref* in individual patients, P0.1*vent* could identify patients above and below these thresholds with reasonable accuracy. A limitation exists in that although the thresholds of P0.1*ref* have been validated, those of P0.1*vent* have not.

These results are encouraging in that they suggest that P0.1 displayed in select ventilators can be used to identify patients with abnormally high and low values. Some caveats remain, however. First, as the authors acknowledge, the thresholds used to set limits on high risk are derived from retrospective analyses of patients with weaning failure. It is not clear whether respiratory muscle output in these patients was the only or main reason for weaning failure. Second, the thresholds selected here apply to only a small fraction of the patients studied; in most patients, P0.1 was between the high and low thresholds, and in such patients the P0.1 results would be equivocal.

Knowledge in physiology in the interpretation of P0.1 is indispensable. In the extremes, as mentioned above, variables that modify P0.1 measurements may create conflicting results regarding the relationship between P0.1 (as an estimate of respiratory drive) and inspiratory muscle pressure output. In the presence of muscle weakness, high chest wall elastance, dynamic hyperinflation, or chest wall–abdominal paradox, a high respiratory drive associated with respiratory distress may yield low inspiratory muscle effort and P0.1 (6). Conversely, a low respiratory drive is not inevitably associated with low inspiratory muscle effort and low P0.1. For example, expiratory muscle recruitment in response to external positive end-expiratory pressure may be associated with high P0.1 despite a weak inspiratory effort (2). Important questions remain: *1*) what is the threshold of inspiratory muscle effort–induced injury, and *2*) does monitoring of P0.1 and inspiratory muscle efforts in critically ill patients receiving mechanical ventilation alter clinical outcomes? Future prospective studies will need to address these questions. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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ORIGINAL ARTICLE

Airway Occlusion Pressure As an Estimate of Respiratory Drive and Inspiratory Effort during Assisted Ventilation

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Abstract

Rationale: Monitoring and controlling respiratory drive and effort may help to minimize lung and diaphragm injury. Airway occlusion pressure (P0.1) is a noninvasive measure of respiratory drive.

Objectives: To determine *1*) the validity of "ventilator" P0.1 (P0.1*vent*) displayed on the screen as a measure of drive, *2*) the ability of P0.1 to detect potentially injurious levels of effort, and *3*) how P0.1*vent* displayed by different ventilators compares to a "reference" P0.1 (P0.1*ref*) measured from airway pressure recording during an occlusion.

Methods: Analysis of three studies in patients, one in healthy subjects, under assisted ventilation, and a bench study with six ventilators. P0.1*vent* was validated against measures of drive (electrical activity of the diaphragm and muscular pressure over time) and P0.1*ref*. Performance of P0.1*ref* and P0.1*vent* to detect predefined potentially injurious effort was tested using derivation and validation datasets using esophageal pressure–time product as the reference standard.

Measurements and Main Results: P0.1*vent* correlated well with measures of drive and with the esophageal pressure–time product (within-subjects $R^2 = 0.8$). P0.1*ref* >3.5 cm H_2O was 80% sensitive and 77% specific for detecting high effort (≥ 200 cm $H_2O \cdot s \cdot min^{-1}$); P0.1*ref* ≤ 1.0 cm H_2O was 100% sensitive and 92% specific for low effort (≤ 50 cm $H_2O \cdot s \cdot min^{-1}$). The area under the receiver operating characteristics curve for P0.1*vent* to detect potentially high and low effort were 0.81 and 0.92, respectively. Bench experiments showed a low mean bias for P0.1*vent* compared with P0.1*ref* for most ventilators but precision varied; in patients, precision was lower. Ventilators estimating P0.1*vent* without occlusions could underestimate P0.1*ref*.

Conclusions: P0.1 is a reliable bedside tool to assess respiratory drive and detect potentially injurious inspiratory effort.

Keywords: artificial respiration; airway occlusion pressure; P0.1; myotrauma; diaphragm

(Received in original form July 20, 2019; accepted in final form February 24, 2020)

*L.B. is Deputy Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

Supported by a salary support grant from the Canadian Institutes for Health Research in the form of a Post-Doctoral Fellowship (I.T.) and Keenan Chair in Critical Care and Acute Respiratory Failure (L.B.).

Author Contributions: I.T., E.C.G., and L.B. designed the study. I.T., D.J., L.C., and L.B. conducted the study and analyzed the data (bench and EFFORT). N.R. and L.B. conducted the study and analyzed the data (APRV/BiPAP). E.C.G. conducted the study and analyzed the data (MYOTRAUMA). L.P. and L.B. conducted the study and analyzed the data (RegAIN). I.T. analyzed all data together. I.T., N.D.F., E.C.G., and L.B. interpreted the results. I.T. and L.B. drafted the manuscript. All authors had full access to all of the study data, contributed to drafting the manuscript or critically revised it for important intellectual content, approved the final version of the manuscript, and took responsibility for the integrity of the data and the accuracy of the data analysis.

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 201, Iss 9, pp 1086–1098, May 1, 2020

Originally Published in Press as DOI: 10.1164/rccm.201907-1425OC on February 25, 2020
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Excessively low and high respiratory drive and inspiratory effort can lead to adverse consequences to the lungs and respiratory muscles and contribute to dyspnea and sleep disturbances, justifying the need for monitoring. Monitoring drive and effort often requires expertise, special equipment, and complex calculations. Airway occlusion pressure (P0.1) is the drop in airway pressure 100 milliseconds after the onset of inspiration during an end-expiratory occlusion of the airway. P0.1 is currently displayed by modern ventilators; however, its validity for estimating drive and effort in ventilated patients remains unknown.

What This Study Adds to the Field: P0.1 displayed by the ventilators correlates with alternative measures of respiratory drive, such as the rate of increase in electrical activity of the diaphragm, and with inspiratory effort measured using the esophageal pressure–time product as the reference standard. Additionally, P0.1 can detect excessive inspiratory effort with reasonable accuracy and low inspiratory effort very accurately using threshold values of 3.5 to 4.0 cm H_2O and 1.0 cm H_2O, respectively. Finally, P0.1 displayed by various ventilators accurately reflects P0.1 measured using a reference method with precision varying according to technical and patient factors (auto–positive end-expiratory pressure).

Respiratory drive represents the intensity of the neural stimulus to breathe. In mechanically ventilated patients, it can be abnormally low (i.e., suppressed or insufficient) or abnormally high (i.e., excessive), and thus result in excessively low or high inspiratory effort, leading to potential injury for the respiratory muscles (i.e., myotrauma) (1–3) or to the lungs (i.e., unintentional patient self-inflicted lung injury) (4–6). A high incidence of abnormal drive (low or high) may explain the high incidence of diaphragm dysfunction at time of separation from mechanical ventilation (7). High drive can also generate dyspnea (8). Additionally, patient–ventilator dyssynchrony is frequently a consequence of abnormal respiratory drive (low or high) (9–12) and is associated with adverse clinical outcomes (10, 13–16). There are, therefore, multiple reasons to monitor and try to control respiratory drive (17) and effort. Monitoring drive and effort is rarely done in clinical practice because it often requires measurement of esophageal pressure (Peso) or electrical activity of the diaphragm (EAdi) and complex calculations, or performing diaphragmatic ultrasound, all of which require time, equipment, and training (18). Therefore, a noninvasive, fast, and feasible measurement is clinically needed.

Airway occlusion pressure (P0.1) is the drop in airway pressure (Paw) 100 milliseconds after the onset of inspiration during an end-expiratory occlusion of the airway (Figure 1) (19). It is, in theory, a reliable measure of respiratory drive because the brevity of the occlusion explains that it is not affected by patient's response to the occlusion and it is independent of respiratory mechanics (20). Moreover, the presence of respiratory muscle weakness, at least up to a certain degree, does not influence P0.1 as a measure of drive (21).

P0.1 has also been correlated with inspiratory effort (22–24) and we recently showed in patients under assisted mechanical ventilation that P0.1 might be able to detect potentially excessive inspiratory effort (25). In this study, P0.1 was measured after activating an end-expiratory occlusion maneuver and by recording the drop in Paw with a pressure sensor at the Y-piece for off-line analysis (reference P0.1 [P0.1*ref*]). P0.1 is now displayed by modern ventilators (ventilator P0.1 [P0.1*vent*]), making it an attractive noninvasive technique for monitoring. However, P0.1*vent* could differ from P0.1*ref* for many reasons, including the site of the pressure measurement (in the ventilator for P0.1*vent* vs. the Y-piece for P0.1*ref*), differences in the algorithm used for the measurement of P0.1*vent* (some perform an occlusion and others do not), and influences of tubing lengths (26).

Therefore, several questions related to the use of P0.1 in critically ill patients remain. Is P0.1 displayed by the ventilator (P0.1*vent*) a valid measure of respiratory drive? In patients with abnormal respiratory mechanics and respiratory muscle dysfunction, what is the relationship between P0.1 and inspiratory effort; and can P0.1 be used to detect potentially excessive and low effort at the bedside? Finally, what is the difference between P0.1*vent* displayed by different ventilators and a reference method to measure P0.1 (P0.1*ref*)? We, therefore, conducted a series of studies (ancillary analyses of three clinical studies in mechanically ventilated patients, one study in healthy subjects, and an original bench study) with the general aim of validating the clinical use of P0.1*vent*.

Methods

Details are shown in the online supplement; aims and design of the study are displayed in Figure 2.

Human Data

Data from three clinical studies and one physiologic study in healthy subjects with measurement of inspiratory effort and drive using Peso and/or EAdi, and P0.1*ref* and/or P0.1*vent*, under assisted ventilation were used: APRV/BiPAP (Effect of Inspiratory Synchronization during Pressure-controlled Ventilation on Lung Distension and Inspiratory Effort) (NCT 02071277), MYOTRAUMA (Diaphragm Injury and Dysfunction during Mechanical Ventilation) (NCT 03108118), EFFORT (Acceptable Range of Inspiratory Effort during Mechanical Ventilation) (NCT 02838524), and RegAIN (Information Conveyed by Electrical Diaphragmatic Activity during Unstressed, Stressed and Assisted Spontaneous Breathing: a Physiological Study) (NCT 01818219). Inclusion and exclusion criteria together with objectives of each study are described in Table E1 in the online supplement. The studies were approved by research ethics boards at each institution and informed consent was obtained from substitute decisionmakers, patients, or healthy subjects. Main or preliminary results were published as full papers or abstracts (25, 27–30).

Patients and healthy subjects. In the clinical studies, critically ill intubated patients under mechanical ventilation for various causes of respiratory failure and patients after cardiac surgery under pressure support or continuous positive Paw were included. The study in healthy subjects enrolled young nonobese males.

Data acquisition. Peso was measured by insertion of a nasogastric tube with an

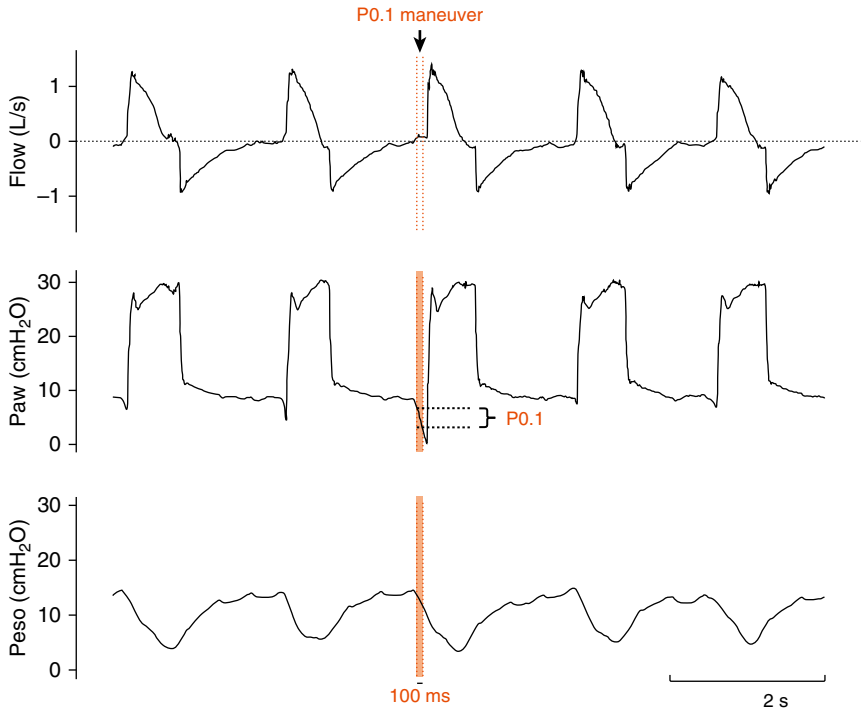

Figure 1. Representative tracing of a patient during an end-expiratory occlusion activated by an airway occlusion pressure (P0.1) maneuver on the Evita-XL ventilator during assisted mechanical ventilation. From top to bottom: $\dot{V}$, airway pressure (Paw), and esophageal pressure (Peso) over time are shown. During the short end-expiratory occlusion (<300 ms), the negative deflection in Paw follows Peso. Minimal positive $\dot{V}$ during the occlusion is seen because of decompression of air in the tubing. P0.1 is the drop in Paw 100 milliseconds after the onset of inspiration during the end-expiratory occlusion.

esophageal balloon as described (31) and EAdi was acquired from built-in electrodes in the nasogastric tube. $\dot{V}$, Paw, Peso and EAdi were recorded using dedicated equipment or the ventilator and stored for analysis.

Procedures. Patients were endotracheally intubated and ventilated with the Evita-XL (Dräger), the Servo-i (Getinge), or the Puritan Bennett 840 (Medtronic) using standard tubing with active humidification. Healthy subjects were ventilated with the Servo-i via a facemask under pressure support with and without added resistance. Each patient or healthy subject was studied in different conditions, each lasting five minutes (details in the online supplement).

In patients, at least three end-expiratory occlusions were performed during each clinical condition by activating the end-expiratory occlusion (Servo-i) or P0.1 maneuver (Evita-XL and Puritan Bennett 840) for offline measurement of P0.1*ref*. P0.1*vent* displayed during the maneuver was recorded from Evita-XL and Puritan Bennett 840. In healthy subjects, P0.1*vent* was directly recorded from the Servo-i ventilator and no occlusion was performed (P0.1*ref* was not measured).

Bench

Specific objectives and overall design of the bench study are described in Table E3.

We tested six ventilators: Servo-i and Servo-u (Getinge), Engström and Carescape R860 (GE Healthcare), Puritan Bennett 840, and Evita-XL. The technique to measure or estimate P0.1*vent* varies between ventilators: *1*) Servo ventilators do not perform an occlusion to measure P0.1*vent*; rather, P0.1*vent* is estimated by extrapolating the drop in Paw during the trigger phase of each breath to 100 milliseconds, and *2*) in the other ventilators, activation of a P0.1 maneuver is followed by an end-expiratory occlusion (<300 ms), and P0.1*vent* is measured during this occlusion with specific criteria (*see* Figure 1).

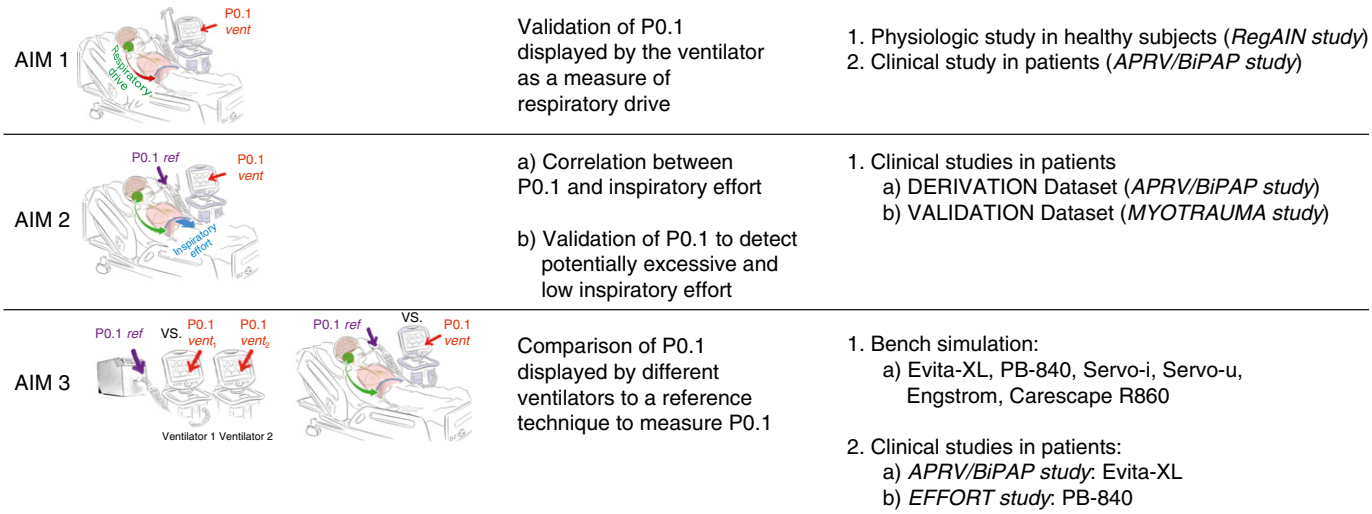

Figure 2. Aims and overall design of the study. Schematic representation is shown displaying the aims of the study and the source of data used to answer each research question. P0.1*ref* is measured at the airway pressure, and P0.1*vent* is displayed by the ventilator. APRV/BiPAP study = Reference 25; EFFORT study = NCT 02838524; MYOTRAUMA study = NCT 03108118; P0.1 = airway occlusion pressure; P0.1*ref* = reference P0.1; P0.1*vent* = ventilator P0.1; PB-840 = Puritan Benett 840; RegAIN study = Reference 29.

Ventilators were connected to a simulator (ASL 5000; Ingmar Medical) and set on pressure support ventilation using a sensitive $\dot{V}$ or pressure trigger. Additional simulations with Servo-u were conducted using a less sensitive pressure trigger, resulting in true short end-expiratory occlusions during the trigger phase.

Lungs with normal and obstructive physiology (for generating auto–positive end-expiratory pressure [auto-PEEP]) were simulated and combined with different patterns of muscular pressure (Pmus) using a linear decay (Servo-i, Servo-u, Engström, Puritan Bennett 840, and Evita-XL), or a nonlinear decay of Pmus in one ventilator that performs an occlusion and one that does not perform an occlusion to measure P0.1 (R860 and Servo-i, respectively) (*see* Tables E4–E7 for details).

During each simulation with the Servo ventilators, three P0.1*vent* values were recorded and three end-expiratory occlusion maneuvers were performed to measure P0.1*ref* offline. In other ventilators, three P0.1 maneuvers were activated and P0.1*vent* recorded. P0.1*ref* was measured offline from Paw tracings during the occlusion (P0.1 maneuver).

$\dot{V}$ and Paw were recorded by a dedicated equipment and stored for analysis.

Data Analysis for Human Data and Bench Study

P0.1. P0.1*ref* was measured from the Paw recordings during end-expiratory occlusion as the drop in Paw from zero $\dot{V}$ until 100 milliseconds (*see* Figure 1) (Acqknowledge 4.3; Biopac Systems). P0.1*vent* was the value of P0.1 displayed by the ventilator. P0.1*ref* and P0.1*vent* are expressed as positive values.

EAdi-derived calculations of drive and inspiratory effort. Maximal EAdi (EAdipeak) was measured as the maximum EAdi per breath. The rate of increase in EAdipeak (EAdipeak/Δt) was calculated as the ratio of EAdipeak over inspiratory time from initial increase in EAdi to first EAdipeak (Acqknowledge 4.3; Biopac Systems). For calculating the rate of increase in Pmus (Pmus/Δt), we first calculated Pmus as the difference between the Peso swing and the product of chest wall elastance and V_T (FluxMed; MBmed SA). Chest wall elastance was estimated based on predicted VC (32). We then calculated Pmus over inspiratory time from initial decrease to peak Pmus. Both EAdipeak/Δt and Pmus/Δt were used as indicators of drive.

Inspiratory effort was measured by the esophageal pressure–time product (PTP) (SR, Sistema Respiratorio). PTP per breath (PTP/br) was the integral of Pmus, from the beginning of inspiratory effort until the end of inspiratory $\dot{V}$ without considering chest wall resistance (33). PTP per minute (PTP/min) was the product of the averaged PTP/br times the respiratory rate. Potentially low inspiratory effort was predefined as PTP/min $\leqslant$50 cm $H_2O \cdot s \cdot min^{-1}$. Two thresholds were used to define potentially excessive effort: $\geqslant$200 cm $H_2O \cdot s \cdot min^{-1}$ and 300 cm $H_2O \cdot s \cdot min^{-1}$. All thresholds were based on previous physiological data (33–40).

Statistical Analysis

Descriptive statistics are expressed as proportions, mean (SD) or median (interquartile range), as appropriate. Normality was assessed by the Shapiro-Wilk test. The average of three P0.1*vent* and three P0.1*ref* values was considered representative of each condition. The coefficient of variation (ratio of SD to the mean) of P0.1*vent* and P0.1*ref* was assessed within each subject in each condition.

The correlations between P0.1*ref* or P0.1*vent* with measures of drive and effort were evaluated using mixed-effects regression models (for repeated measures). The ability of P0.1*ref* and P0.1*vent* to detect potentially excessive and low effort was assessed using the area under the receiver operating characteristics curve (AUROC). The best cutoffs were selected based on the Youden index (sensitivity + specificity -1). Sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values were calculated using standard equations (41). APRV/BiPAP was used as the derivation cohort and MYOTRAUMA was used as the validation dataset to establish optimal cutoff values for P0.1*ref*.

Accuracy of P0.1*vent* compared with P0.1*ref* was assessed by Bland-Altman plots (42) for each ventilator, considering the trigger sensitivity and auto-PEEP. For Servo ventilators, proportional bias was calculated (42). Within-patient limits of agreement were calculated using mixed-effects models.

Statistical analysis was performed using Stata/IC 15.0 (StataCorp) and R version 3.5.3 (www.R-project.org).

Results

Clinical characteristics of patients and healthy subjects are shown in Table 1. Description of inspiratory effort and respiratory drive measured in healthy subjects, patients, or simulated in the bench are shown in Table 2.

P0.1*vent* As a Measure of Respiratory Drive

In healthy subjects, P0.1*vent* (Servo-i) correlated with EAdipeak and EAdipeak/Δt (between-subjects $R^2 = 0.51$ and 0.39, respectively; within-subjects $R^2 = 0.68$ and 0.75, respectively). In all subjects (healthy and patients), P0.1*vent* (Servo-i and Evita-XL) also correlated with Pmus/Δt (between-subjects $R^2 = 0.38$ and within-subjects $R^2 = 0.90$) (Figure 3).

Correlation between P0.1 and Inspiratory Effort

In patients, the correlation between P0.1*ref* and PTP/min was strong (between-patients $R^2 = 0.67$ and within-patients $R^2 = 0.86$); the correlation was weaker for PTP/br (between-patients $R^2 = 0.15$ and within-patients $R^2 = 0.85$) (*see* Figure 3).

In healthy subjects, P0.1*vent* (Servo-i) correlated with PTP/min (between-subjects $R^2 = 0.47$ and within-subjects $R^2 = 0.84$). In patients, P0.1*vent* (Evita-XL) also correlated with PTP/min (between-patients $R^2 = 0.25$ and within-patients $R^2 = 0.85$) (*see* Figure 3).

P0.1 to Detect Potentially Excessive and Low Inspiratory Effort

Respiratory effort fell below 50 cm $H_2O \cdot s \cdot min^{-1}$ in 16% of the recordings, and exceeded 200 cm $H_2O \cdot s \cdot min^{-1}$ and 300 cm $H_2O \cdot s \cdot min^{-1}$ in 28% and 11% of recordings, respectively. Diagnostic performance of P0.1*ref* and P0.1*vent* (Evita-XL) and optimal thresholds to detect potentially injurious effort are displayed in Table 3 and Figure 3.

For potentially excessive effort using a cutoff of PTP/min $\geqslant$200 cm $H_2O \cdot s \cdot min^{-1}$, validation of the published threshold of P0.1*ref* $>$3.5 cm H_2O (25) in an independent dataset showed a sensitivity of 80% and specificity of 74%. For a cutoff

Table 1. Clinical Characteristics of Healthy Subjects and Patients

	Healthy Subjects (from the RegAIN Study)	Patients		
		Derivation Dataset (from APRV/BiPAP Study)	Validation Dataset (from MYOTRAUMA Study)	Additional Data to Test Accuracy of PB-840 in Patients (from EFFORT Study)
Patients, *n*	13	11	15	21
Tracings, *n*	49	28	46	42
Tracings per patient, median (minimum–maximum)	4 (2–4)	3 (1–3)	3 (1–6)	2
Age, yr, mean (SD)	25 (4)	55 (11)	54 (19)	64 (8)
Sex, F, *n* (%)	0 (0)	3 (27)	7 (47)	4 (19)
Diagnosis, *n* (%)				
Pneumonia	—	2 (18)	2 (15)	0 (0)
Nonpulmonary sepsis	—	4 (36)	3 (20)	0 (0)
Postoperative (noncardiac)	—	0 (9)	5 (33)	0 (0)
Respiratory failure (other)	—	4 (36)	5 (33)	0 (0)
Heart failure	—	1 (9)	0 (0)	0 (0)
Postoperative cardiac surgery	—	0 (0)	0 (0)	21 (100)
Arterial gas, mm Hg, mean (SD)				
Pa_{O_2}/FI_{O_2}	—	218.1 (68.7)	228.8 (91.8)	303.7 (101.5)
Pa_{O_2}	—	99 (28)	96 (33)	155 (47)
Pa_{CO_2}	—	49 (11)	42 (7)	41 (7)
pH	—	7.38 (0.06)	7.41 (0.05)	7.35 (0.06)
Sedation, *n* (%)				
Sedation–agitation score	—	2 (2–3)	2 (1–3)	4 (3–4)
Use of continuous sedation	—	13 (46)	N/A	0 (0)
Use of continuous opioids	—	9 (32)	N/A	0 (0)
Previous use of continuous NMBA	—	N/A	4 (8)	0 (0)
Ventilation mode, *n* (%)				
PC-CMV	—	10 (36)	15 (33)	0 (0)
PC-SIMV	—	10 (36)	0 (0)	0 (0)
PC-IMV	—	8 (29)	0 (0)	0 (0)
PS	49 (100)	0 (0)	31 (67)	21 (50)
CPAP 0*	—	0 (0)	0 (0)	21 (50)

Definition of abbreviations: APRV/BiPAP study = Reference 25; CPAP = continuous positive airway pressure; EFFORT study = NCT 02838524; MYOTRAUMA study = NCT 03108118; N/A = not available; NMBA = neuromuscular blocking agent; PB-840 = Puritan Bennett 840; PC-CMV = pressure assist-control; PC-IMV = pressure control intermittent mandatory ventilation; PC-SIMV = pressure control spontaneous intermittent mandatory ventilation; PS = pressure support; RegAIN study = Reference 29.
*CPAP 0 represents spontaneous breathing with no pressure.

of PTP/min $\geq$300 cm $H_2O \cdot s \cdot min^{-1}$, derivation and validation AUROC (95% confidence interval [CI]) for P0.1*ref* was 0.92 (0.76–1.00) and 0.96 (0.85–1.00), respectively; and best thresholds were 3.9 cm H_2O in derivation and 4.7 in validation datasets, respectively (sensitivity of 100% and specificities 80–92%).

For potentially low effort using a cutoff of PTP/min $\leq$50 cm $H_2O \cdot s \cdot min^{-1}$, P0.1*ref* showed an excellent discriminative accuracy (derivation AUROC, 0.97 [95% CI, 0.82–1.00]; validation AUROC, 0.97 [95% CI, 0.88–1.00]; *see* Figure 3). In both, the best threshold was 1.1 cm H_2O (sensitivity 100% and specificity 92%).

For a cutoff of PTP/min $\geq$200 cm $H_2O \cdot s \cdot min^{-1}$, P0.1*vent* (Evita-XL) showed an AUROC of 0.81 (0.63–0.94); P0.1*vent* >3.5 cm H_2O had a sensitivity of 67% and a specificity of 86%; and the best threshold was 4.0 cm H_2O (sensitivity 67% and specificity 91%). For a cutoff of PTP/min $\leq$50 cm $H_2O \cdot s \cdot min^{-1}$, the AUROC was 0.92 (0.76–0.99) and the best threshold was 1.3 cm H_2O (sensitivity 100% and specificity 88%).

P0.1*vent* Displayed by Different Ventilators Compared with P0.1*ref*

Mean bias and limits of agreement of P0.1*vent* compared with P0.1*ref* are presented in Table 4. Bland-Altman plots are displayed in Figures 4, E2, and E3.

Bench. A total of 305 simulations were analyzed. Median (interquartile range) P0.1*ref* in the bench was 1.8 (0.8–3.7) cm H_2O and the corresponding P0.1*vent* was 1.7 (1.0–3.1) cm H_2O. The coefficient of variability of P0.1*vent* in repeated measures within each simulation was minimal (0–6%).

Table 2. Breathing Effort and Respiratory Drive in Healthy Subjects, Patients, and Bench Simulation

		Patients			
	Healthy Subjects (from the RegAIN Study)*	Derivation Dataset (from the APRV/BiPAP Study)*	Validation Dataset (from the MYOTRAUMA Study)	Additional Data to Test Accuracy of PB-840 in Patients (from the EFFORT Study)	Bench Simulation*
Respiratory drive and effort					
P0.1*vent*†, cm H_2O	0.7 (0.6–1.0)	1.9 (0.6–3.2)	—	3.5 (1.7–5.3)	1.7 (1.0–3.1)
P0.1*vent*†, cm H_2O, minimum–maximum	0.2–2.7	0.1–5.5	—	0.1–7.5	0–10.7
P0.1*ref*‡, cm H_2O	—	2.0 (1.3–2.8)	3.2 (1.8–4.6)	3.0 (1.7–4.4)	1.8 (0.8–3.7)
P0.1*ref*‡, cm H_2O, minimum–maximum	—	0.3–3.9	0.0–12.0	0.5–7.0	0.1–10.5
EAdipeak§, μV	12 (7–16)	—	—	—	—
EAdipeak/Δt§, $\mu V \cdot s^{-1}$	7.8 (5.7–11.3)	—	—	—	—
Pmus‖, cm H_2O	10.0 (7.2–13.2)	8.8 (6.0–14.2)	—	—	—
Pmus/Δt‖, cm $H_2O \cdot s^{-1}$	6.7 (4.0–8.6)	11.7 (8.3–25.4)	—	—	—
PTP/br, cm $H_2O \cdot s$	9.6 (5.7–15.5)	5.8 (3.5–8.1)	6.6 (3.2–10.0)	—	—
PTP/min, cm $H_2O \cdot s \cdot min^{-1}$	120.4 (80.1–200.8)	103.6 (42.3–165.0)	137.7 (69.3–206.1)	—	—
Mechanics					
Presence of auto-PEEP¶, *n* (%)	—	24 (57)	13 (28)	22 (52)	147 (48)
PEEPi value**, cm H_2O	—	1.5 (1.3–2.5)	1.6 (1.2–5.2)	1.9 (1.4–2.3)	4.4 (3.0–5.9)

Definition of abbreviations: APRV/BiPAP study = Reference 25; EAdipeak = maximal electrical activity of the diaphragm; EAdipeak/Δt = rate of increase in EAdipeak; EFFORT study = NCT 02838524; MYOTRAUMA study = NCT 03108118; P0.1*vent* = ventilator airway occlusion pressure; P0.1*ref* = reference airway occlusion pressure; PB-840 = Puritan Bennett 840; PEEP = positive end-expiratory pressure; PEEPi = intrinsic positive end-expiratory pressure; Pmus = muscular pressure; Pmus/Δt = rate of increase in Pmus; PTP/br = pressure–time product per breath; PTP/min = pressure–time product per minute; RegAIN study = Reference 29.

All distributions are reported as median (interquartile range) unless otherwise stated.

*For each dataset, P0.1*vent* was displayed by the following ventilators: in RegAIN, Servo-i (Getinge); in APRV/BiPAP, Evita-XL (Dräger); and in EFFORT, Puritan Bennett 840 (Medtronic); and in the bench simulation by Servo-i and Servo-u (Getinge), Engström and Carescape R860 (GE Healthcare), Puritan Bennett 840, and Evita-XL.

†P0.1*vent* not available in MYOTRAUMA study.

‡P0.1*ref* not measured in healthy subjects, given the lack of occlusion.

§Electrical activity of the diaphragm-derived parameters only measured in healthy subjects.

‖Pmus/Δt measured in healthy subjects and derivation dataset to compare with P0.1*vent*.

¶In the bench simulation, auto-PEEP was defined as the presence of PEEPi ⩾ 0.5 cm H_2O; in the patients, it was defined as the presence of PEEPi ⩾ 1.0 cm H_2O.

**Considering tracings with auto-PEEP.

For Evita-XL and Puritan Bennett 840, accuracy and precision were excellent. For Engström and R860 bias was low whatever the Pmus profile but, lacking decimal values, precision was lower. In Evita-XL, Puritan Bennett 840, Engström, and R860 no difference of precision across the range of P0.1 values or influence of auto-PEEP was observed.

Mean bias for Servo ventilators was low (<0.5 cm H_2O) and slightly negative (i.e., sometimes underestimating P0.1*ref*) with large limits of agreement (∼2.0 cm H_2O). Underestimation worsened at high values of P0.1 and with auto-PEEP. Accuracy and precision of Servo-u improved using pressure trigger with a lower sensitivity. Bias of Servo-i using a nonlinear decay of Pmus was larger and more negative with a lower precision.

Human data. In patients, median (interquartile range) P0.1*ref* was 2.5 (1.4–3.6) cm H_2O and P0.1*vent* was 2.7 (0.8–4.6) cm H_2O; coefficients of variation were 17 (9–31%) and 26 (15–40%), respectively.

Accuracy of P0.1*vent* compared with P0.1*ref* in patients ventilated with Evita-XL and Puritan Bennett 840 showed a low bias (0.0 and 0.3 cm H_2O, respectively), but limits of agreement were larger than in the bench (∼1.5 cm H_2O for both).

Discussion

Our results provide useful information on the validity of P0.1*vent* and reliability of P0.1 to estimate inspiratory effort. First, P0.1*vent* correlates with alternative measures of respiratory drive. Second, P0.1*vent* and P0.1*ref* correlate with inspiratory effort and detect excessive inspiratory effort with reasonable accuracy and low inspiratory

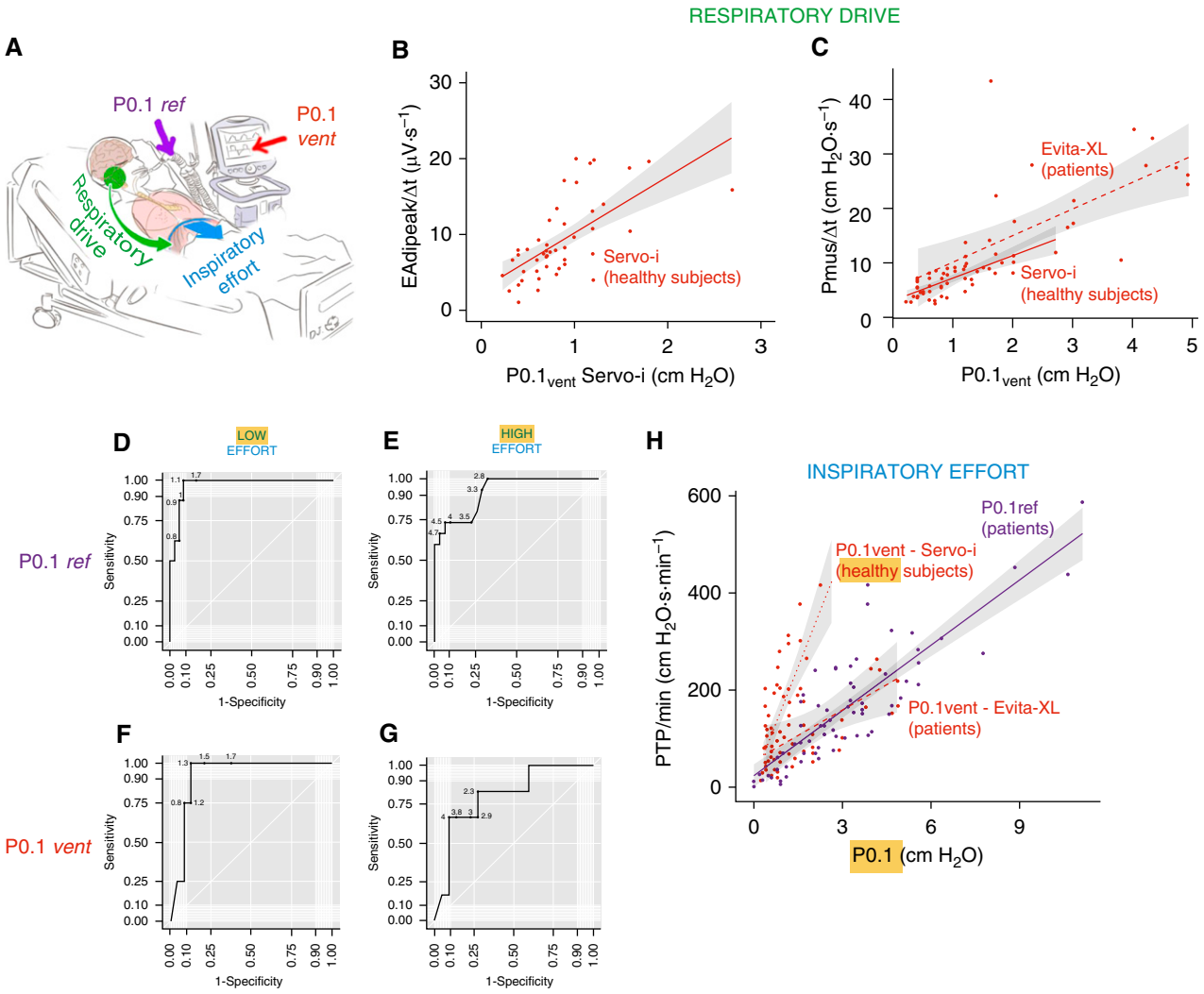

Figure 3. Airway occlusion pressure (P0.1) as a measure of respiratory drive and inspiratory effort per minute. (*A*) Schematic representation of the relationship between respiratory drive and inspiratory effort in an intubated patient, and the difference between the reference P0.1 (P0.1*ref*) measured at the airway pressure close to the Y-piece and the ventilator P0.1 (P0.1*vent*) displayed on the screen of the ventilator. *B* and *C* display the correlation between P0.1*vent* and alternative measures of respiratory drive (rate of increase in electrical activity of the diaphragm [EAdipeak/Δt] and muscular pressure [Pmus/Δt], respectively). Each dot corresponds to a patient or healthy subject in a clinical condition. Regression lines are drawn in red, and shaded gray areas correspond to 95% confidence intervals (CIs). *B* corresponds to the RegAIN study ($N = 49$ tracings in 13 patients; between-subjects $R^2 = 0.39$ and within-subjects $R^2 = 0.75$). (*C*) Data from the APRV/BiPAP and the RegAIN studies (References 25 and 29, respectively) are pooled together ($N = 69$ tracings in 22 patients; between-subjects $R^2 = 0.38$, and within-subjects $R^2 = 0.90$). (*D–G*) Discriminative accuracy of P0.1*ref* and P0.1*vent* to detect potentially injurious inspiratory effort per minute ($\leq$50 cm $H_2O \cdot s \cdot min^{-1}$ and $\geq$200 cm $H_2O \cdot s \cdot min^{-1}$). (*D* and *E*) Validation dataset (MYOTRAUMA study [NCT 03108118]) for P0.1*ref* (area under the receiver operating characteristics curve [AUROC], 0.97 [95% CI, 0.88–1.00] for low effort per minute and AUROC, 0.91 [95% CI, 0.79–0.98] for high effort per minute). (*F* and *G*) Derivation dataset (APRV/BiPAP study) for P0.1*vent* (Evita-XL) (AUROC, 0.92 [95% CI, 0.76–0.99] for low effort per minute and AUROC, 0.81 [95% CI, 0.76–0.99] for high effort per minute). (*H*) Relationship between effort per minute and P0.1. Each dot corresponds to a patient or healthy subject in a clinical condition ($N = 143$ tracings in 37 subjects). The relationship between esophageal pressure–time product per minute (PTP/min) and P0.1*ref* is represented in purple (data from APRV/BiPAP and MYOTRAUMA studies), the regression line is continuous, and the shaded gray area corresponds to 95% CI (between-patient $R^2 = 0.67$ and within-patient $R^2 = 0.86$). The relationship between PTP/min and P0.1*vent* is represented in red, the regression line is dashed for data corresponding to the APRV/BiPAP study (patients connected to Evita-XL) and dotted for data corresponding to RegAIN (healthy subjects connected to Servo-i). The shaded gray area corresponds to 95% CI (between-patients $R^2 = 0.25$, within-patients $R^2 = 0.85$ for patients and between-subjects $R^2 = 0.47$, and within-subjects $R^2 = 0.84$ for healthy subjects).

effort very accurately. Third, P0.1*vent* displayed by various ventilators accurately reflects P0.1*ref* with precision varying according to technical and patient factors (auto-PEEP) but being generally excellent. Therefore, threshold values of P0.1*ref* for excessive (3.5–4.0 cm H_2O) and low inspiratory effort (1.1 cm H_2O) carefully validated in this study can be extrapolated to the clinical setting using similar values for P0.1*vent* displayed by different ventilators considering its technical specificities.

P0.1 As a Measure of Respiratory Drive and Effort

Respiratory drive is the intensity of the neural stimulus to breathe that controls the magnitude of inspiratory effort. P0.1 is a measure of respiratory drive shown, for

Table 3. Diagnostic Performance of Threshold Values of P0.1 Measured at the Airway Pressure and P0.1 Displayed by the Ventilator to Detect Potentially Injurious Effort

	PTP/min ($cm\ H_2O \cdot s \cdot min^{-1}$)	AUROC (95% CI)	P0.1 Threshold ($cm\ H_2O$)	Sensitivity	Specificity	Diagnostic Accuracy	+LR	−LR	PPV	NPV
P0.1*ref*, high effort	200									
Validation dataset		0.91 (0.79–0.98)								
Published			3.5	0.80	0.77	0.78	3.54	0.26	0.63	0.89
Best*			2.8	1.00	0.68	0.78	3.10	0.32	0.60	1.00
P0.1*ref*, high effort	300									
Derivation dataset		0.92 (0.76–0.99)								
Best*			3.9	1.00	0.92	0.93	12.5	0.00	0.50	1.00
Validation dataset		0.96 (0.85–0.99)								
Best in derivation			3.9	1.00	0.80	0.83	5.00	0.00	0.43	1.00
Best*			4.7	1.00	0.88	0.89	8.33	0.00	0.55	1.00
P0.1*ref*, low effort	50									
Derivation dataset		0.97 (0.82–1.00)								
Best*			1.1	1.00	0.92	0.93	12.00	0.00	0.67	1.00
Validation dataset		0.97 (0.88–1.00)								
Best*			1.1	1.00	0.92	0.93	13.00	0.00	0.73	1.00
P0.1*vent*†, high effort	200									
Derivation dataset		0.81 (0.63–0.94)								
Published for P0.1*ref*			3.5	0.67	0.86	0.82	4.89	0.39	0.57	0.91
Best*			4.0	0.67	0.91	0.86	7.33	0.37	0.67	0.91
P0.1*vent*†, low effort	50									
Derivation dataset		0.92 (0.76–0.99)								
Best for P0.1ref			1.1	0.75	0.95	0.89	9.00	0.27	0.6	0.96
Best*			1.3	1.00	0.88	0.89	8.00	0.12	1.00	1.00

Definition of abbreviations: AUROC = area under the receiver operating characteristics curve; CI = confidence interval; FN = false negative; FP = false positive; LR = likelihood ratio; NPV = negative predictive value; P0.1 = airway occlusion pressure; P0.1*ref* = reference airway occlusion pressure; P0.1*vent* = ventilator airway occlusion pressure; PPV = positive predicted value; PTP/min = pressure–time product per minute; TN = true negative; TP = true positive.

Sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); diagnostic accuracy = (TP + TN)/(TP + TN + FP + FN); +LR = sensitivity/(1-specificity); −LR = (1-sensitivity)/specificity; PPV = TP/(TP+FP); NPV = TN/(TN+FN).

*Best threshold corresponding to the highest Youden index (sensitivity + specificity −1). Validation dataset corresponds to randomly selected tracings from MYOTRAUMA study (NCT 03108118) and derivation dataset to selected tracings from APRV/BiPAP study (Reference 25).

†Evita-XL was used in the APRV/BiPAP dataset.

instance, to be sensitive to CO_2 removal during venovenous extracorporeal membrane oxygenation in critically ill patients (43). We show in this study that P0.1 directly displayed by the ventilator (P0.1*vent*) correlates with alternative measures of respiratory drive (*see* discussion in the online supplement).

There is a tight correlation between P0.1*vent* and P0.1*ref* with inspiratory effort. This has been also shown in previous studies in which P0.1 was measured with different techniques, such as doing an occlusion at the Y-piece (24), using the trigger phase of old ventilators and measuring it offline (23), or as the drop in Peso during the first 100 milliseconds of inspiratory effort (22). Our findings are consistent with the positive correlation described by Bellani and colleagues (44) between P0.1*vent* and $\dot{V}_{O_2}$ due to varying loads on the respiratory muscles. We found a tighter correlation for P0.1*ref* and P0.1*vent* with effort (both per breath and per minute) within-patients than between-patients that is explained by the different degrees of derangements in respiratory mechanics and muscle function across patients (7, 45). Those modify the individual relationship between respiratory drive (i.e., P0.1) and effort.

Correlation of P0.1*ref* and P0.1*vent* with effort per minute was better compared with the effort per breath, suggesting that critically ill patients might also increase their respiratory rate in response to drive in the context of frequent respiratory muscle weakness limiting their ability to increase tidal effort (21, 34, 46, 47). Dissociation between a high drive (due to high brain input) and a low efficiency in terms of effort generated (due to respiratory muscle weakness) results in dyspnea. Monitoring dyspnea during mechanical ventilation merits urgent attention (48, 49) and P0.1 was shown to correlate with dyspnea in patients with chronic respiratory diseases (50–52). Use of P0.1*vent* for this purpose might be tested in future studies of patients under assisted ventilation.

P0.1 to diagnose potentially injurious effort. P0.1 cannot universally give a precise estimate of effort for all patients as a whole (given the lower correlation between P0.1 and effort between patients, as discussed); however, it can still be a valuable technique to detect extremes of effort, which we

Table 4. Agreement between P0.1 Displayed by Each Ventilator and Reference Method to Measure P0.1

Ventilator	*n**	Type of Decay in Pmus	Auto-PEEP† [*n* (%)]	Bias (*cm H_2O*) (95% CI)	Limits of Agreement‡ (*cm H_2O*)	Proportional Bias§ (%) (95% CI)	Proportional Limits of Agreement§ (%)
Bench simulation							
Evita-XL	48	Linear	24 (50)	0.3 (0.2–0.3)	−0.3 to 0.8	—	—
PB-840	48	Linear	22 (46)	0.1 (0.1 to 0.2)	−0.2 to 0.4	—	—
GE Engström	45	Linear	21 (47)	0.3 (0.1 to 0.5)	−1.0 to 1.6	—	—
GE Carescape R860	32	Nonlinear	14 (44)	−0.1 (−0.4 to 0.1)	−1.4 to 1.2	—	—
Servo-i							
Sensitive trigger	48	Linear	23 (48)	−0.3 (−0.6 to -0.1)	−2.2 to 1.5	−5.2 (−15.7 to 5.2)	−75.8 to 65.3
Sensitive trigger	36	Nonlinear	18 (50)	−1.1 (−1.5 to -0.7)	−3.6 to 1.4	−33.4 (−43.5 to −23.3)	−91.9 to 25.1
Servo-u							
Sensitive trigger	48	Linear	24 (50)	−0.4 (−0.7 to -0.3)	−1.8 to 0.9	−13.3 (−23.1 to −3.4)	−79.6 to 53.0
Low sensitive pressure trigger	23	Linear	0 (0)	−0.1 (−0.2 to 0.0)	−0.5 to 0.3	—	—
Patients†							
Evita-XL	28	—	13 (46)	0.0 (−0.3 to 0.3)	−1.6 to 1.6	—	—
PB-840	42	—	22 (52)	0.3 (0.0 to 0.5)	−1.2 to 1.8	—	—

Definition of abbreviations: CI = confidence interval; P0.1 = airway occlusion pressure; PB-840 = Puritan Bennett 840; PEEP = positive end-expiratory pressure; Pmus = muscular pressure.

**n* = number of simulations (bench) and tracings (patients) included. As detailed in the online supplement, the total number of simulations performed for each ventilator with a sensitive trigger using a linear decay in Pmus was 48 and with a nonlinear decay in Pmus was 36. There were 24 simulations performed in the Servo-u using a less sensitive pressure trigger. Some simulations were discarded owing to ineffective efforts and technical issues.

†In the bench simulation, auto-PEEP was defined as the presence of intrinsic PEEP ⩾ 0.5 cm H_2O; in the patients it was defined as the presence of intrinsic PEEP ⩾ 1.0 cm H_2O.

‡Within-patient repeatability limits were calculated to account for repeated measures in patients using a linear mixed-effects model.

§Proportional bias and limits of agreement was only calculated for experiments in which an increase in variability of the difference between P0.1 displayed by the ventilator and the reference P0.1 measured from airway pressure recording was observed as the magnitude of the measurement increased.

validated in the current study. We have previously shown that a P0.1*ref* higher than 3.5 cm H_2O (25) has a good sensitivity and specificity to diagnose potentially excessive inspiratory effort, and we have validated it in this study. The same threshold was proposed by Alberti and colleagues for excessive work of breathing (22). Additionally, we describe a new reliable threshold for P0.1*ref* higher than 4.0 cm H_2O if excessive effort is considered to be that higher than 300 cm $H_2O \cdot s \cdot min^{-1}$. A P0.1*ref* lower than 1.1 cm H_2O showed an excellent accuracy to diagnose low inspiratory effort in our derivation and validation datasets.

We tested the use of P0.1*vent* to diagnose extremes of effort using the Evita-XL. Diagnostic accuracy of P0.1*vent* to detect excessive inspiratory effort is good though slightly lower than with P0.1*ref*. It remains, however, excellent for detecting low effort. Thresholds of P0.1*ref* to detect excessive and low effort can be used as a reference for other ventilators, considering the technique used by the ventilator (short occlusion vs. estimation based on the trigger phase) and the differences between P0.1*vent* and P0.1*ref* shown in the bench and patients. Positive predictive values of the selected thresholds in the context of relatively low absolute frequency of extremes of effort is limited; therefore, they should be used as warning signs and interpreted in the clinical context.

How did we determine thresholds for potentially injurious effort? Observational data suggest that an intermediate range of inspiratory effort might be warranted (1, 53). The boundaries that should be considered for excessive and low effort for most patients is yet to be established. Load-induced diaphragm injury is present in animal models and humans breathing close to fatiguing thresholds (54, 55). At the end of a failed spontaneous breathing trial (SBT), patients are close to reaching this threshold and exhibit clinical signs of respiratory distress or discomfort, resulting in resumption of ventilation by clinicians (56). During a successful SBT, effort is lower and can be sustained indefinitely at this level after extubation (57). Therefore, a safe potentially noninjurious upper threshold of effort is represented by the upper limit of effort during successful SBTs. We are not proposing P0.1 as a weaning index to detect failure, but we simply reasoned from these measurements that a load higher than this level may be difficult to sustain without risk of diaphragm injury. Because the risk of injury due to excessive effort might vary according to patient's susceptibility (2, 6) and muscle function, we selected two thresholds from the available data (33, 34, 37–40), summarized in Table E2 for excessive effort: 200 and 300 cm $H_2O \cdot s \cdot min^{-1}$. Given the limited number of observations available for P0.1*vent*, we could reliably test only the lower, 200 cm $H_2O \cdot s \cdot min^{-1}$. On the other end of the spectrum, we selected inspiratory effort below 50 cm $H_2O \cdot s \cdot min^{-1}$ because it has been associated with ineffective efforts (35) and prolonged insufflation under

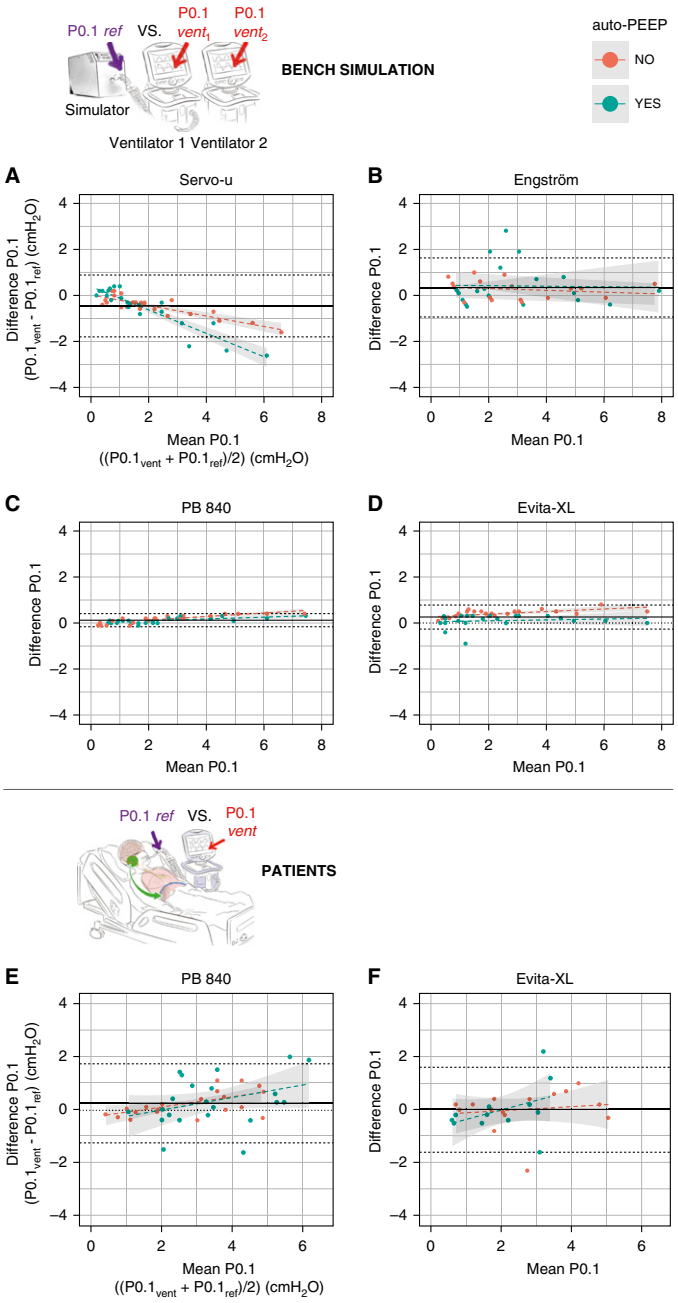

Figure 4. Bland-Altman plots showing accuracy and precision of airway occlusion pressure (P0.1) displayed as ventilator P0.1 (P0.1*vent*) compared with reference P0.1 (P0.1*ref*) measured at the airway pressure. The difference between P0.1*vent* and the corresponding P0.1*ref* is plotted against the average of the two variables. Black horizontal continuous lines represent mean bias, and dashed lines represent the upper and lower limits of agreement. Orange and green dots represent simulations without and with intrinsic positive end-expiratory pressure (auto-PEEP), respectively. Regression line for the difference between P0.1*vent* and P0.1*ref* across the range of P0.1 values are plotted with 95% confidence interval for simulations with and without intrinsic PEEP. The same simulated inspiratory effort (linear decay in muscular pressure) and lung model were run with each ventilator in the bench study: (*A*) Servo-u (Getinge), (*B*) Engström (GE Healthcare), (*C*) PB-840 (Medtronic), and (*D*) Evita-XL (Dräger). (*E*) Data from the EFFORT study (NCT 02838524) in which Puritan Bennett 840 was used and (*F*) data from APRV/BiPAP (Reference 25) study in which Evita-XL was used. PB-840 = Puritan Benett 840.

pressure support (36), both suggesting overassistance and insufficient effort (53), potentially resulting in disuse atrophy. Chosen thresholds for potentially excessively high and low effort need further refinements considering a patient's individual risk of injury (e.g., presence of sepsis) (2) and individual muscular strength but are probably reasonable as a warning indicator and helpful for clinicians. Detection of these thresholds with P0.1 could prompt for performing more direct measurements of efforts.

Respiratory rate is also correlated with inspiratory effort per minute (data not shown) because the mathematical relationship between both parameters and extreme values of rate might serve to detect extremes values of drive or effort (53). However, respiratory rate is insensitive to changes in drive and effort within a wide range of values (58, 59), indicating it is useless for titrating interventions.

Comparison between P0.1vent displayed by different ventilators and P0.1ref. The mean difference between P0.1*vent* and P0.1*ref* is small across ventilators but precision varies between ventilators because of technical and patient factors, including the performance of an occlusion, trigger sensitivity, use of decimal, presence of auto-PEEP, shape of Pmus, and tubing length (26). Servo ventilators estimate P0.1 by extrapolating the drop in Paw during the trigger phase to 100 milliseconds (*see* Figure E4), whereas others need activating a maneuver resulting in an occlusion (*see* Figure 1) (60). The difference between P0.1*vent* and P0.1*ref* for the Servo ventilators increases at high effort with underestimation of P0.1*ref* (i.e., P0.1*ref* $>$ 2.0 cm H_2O) because trigger delay (brief occlusion) shortens with strong efforts, (i.e., $<$50 ms) (61). Using pressure trigger with lower sensitivity generates a longer occlusion that corrects the underestimation. Underestimation is further worsened by nonlinear decay of Pmus in Servo ventilators because extrapolation of the initial drop in Paw assumes a linear decay of Pmus.

Auto-PEEP can lead to underestimation of P0.1*ref* in Servo ventilators because of the time lag generated, resulting in further separation of Paw and Pmus. Auto-PEEP does not result in underestimation of P0.1*ref* when an

occlusion is performed because $\dot{V}$ returns to zero before the measurement. In the clinical setting, auto-PEEP may decrease the accuracy of P0.1 as an index of drive, depending on the magnitude of hyperinflation and the shape of inspiratory muscle pressure (62). However, in intubated patients with auto-PEEP, Conti and colleagues showed that P0.1 measured from zero $\dot{V}$ estimates the drop in Peso during the first 100 milliseconds of the effort reasonably well with only a small bias (-0.3 ± 0.5 cm H_2O) (63). Additionally, P0.1 correlates with inspiratory effort in intubated patients with auto-PEEP (23).

In patients, accuracy of P0.1*vent* displayed by Evita-XL and Puritan Bennett 840 compared with P0.1*ref* were excellent but precision was slightly poorer than in the bench, consistent with previous data (60). Possible reasons for this include higher compressible volume, humidity in the tubing, or leaks.

Strengths and weaknesses. This study includes healthy subjects, patients under assisted ventilation of various severity, and a bench model, allowing testing of P0.1 over a wide range of inspiratory effort. Patient data allowed for direct validation of P0.1*vent* as a measure of drive, detecting excessive and low effort, and for understanding the limitations of P0.1*vent* at the bedside. The bench model allowed for replicability of simulations in various ventilators and conditions, and for systematic assessment of the influence of trigger sensitivity, auto-PEEP, and patterns of effort.

Limitations of our study include the lack of clinical outcomes, relatively arbitrary thresholds for low and high efforts, and lack of information regarding specific populations (e.g., morbidly obese patients). Additionally, other clinical variables that help to define excessive effort, such as self-evaluation or heteroevaluation of breathlessness, signs of respiratory distress, and worsening mechanics were missing, as well as information regarding respiratory muscle function. Auto-PEEP was relatively small in the patients. Moreover, relaxation of expiratory muscles at the beginning of inspiration, often present with high drive, can contribute to P0.1; the specific influence of this phenomenon on P0.1 was not studied. Additionally, correlation between P0.1*vent* and EAdipeak/Δt as an independent measure of respiratory drive was performed only in healthy subjects. However, the Pmus/Δt, another measure of drive that reflects the activation of all respiratory muscles, was correlated with P0.1*vent* both in patients and in healthy subjects, showing similar results in both groups. Lastly, threshold values for P0.1*ref* to detect potentially injurious effort were tested in derivation and validation datasets, but P0.1*vent* was only tested in one dataset of patients. P0.1*ref* was a standardized way to measure P0.1 in our study, whatever the ventilator used. We, therefore, provide an extensive description of how P0.1*ref* differs from P0.1*vent* across ventilators. This will allow clinicians to adapt the values provided by the ventilator they use in clinical practice.

Conclusions

Changes in P0.1*vent* accurately predict changes in respiratory drive and the tight within-patient correlation between P0.1*vent* and the esopphageal pressure–time product also allows clinicians to follow patient's changes in effort. P0.1 can be used to detect low inspiratory effort with excellent accuracy and high effort reasonably well using thresholds of 1.0 and 3.5 to 4.0 cm H_2O, respectively. When using P0.1*vent* from different ventilators, differences with P0.1*ref* should be considered. For ventilators without true occlusions, P0.1*ref* can be underestimated with high inspiratory effort (i.e., P0.1 $>$ 2.0 cm H_2O) and with auto-PEEP when using a sensitive $\dot{V}$ trigger.

With increased awareness that extremes of effort are potentially injurious for the diaphragm (3) and lung (4), P0.1*vent* provides a noninvasive tool to monitor interventions that aim at controlling drive and effort. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the Methods in Epidemiologic, Clinical, and Operations Research (MECOR) program from Latin America and the American Thoracic Society for their methodological support.

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Figure legends

Figure 1 Representative tracing of a patient during an end-expiratory occlusion activated by a P0.1 manoeuvre on the Evita-XL during assisted mechanical ventilation. From top to bottom flow, airway pressure (Paw) and esophageal pressure (Peso) over time. During the short end-expiratory occlusion (< 300 ms) the negative deflection in Paw follows Peso. Minimal positive flow during the occlusion is seen due to decompression of air in the tubing. Airway occlusion pressure (P0.1) is the drop in airway pressure 100 ms after the onset of inspiration during the end-expiratory occlusion.

Abbreviations: Paw= airway pressure, Peso = esophageal pressure, P0.1 = airway occlusion pressure.

Figure 2 Aims and overall design of the study

Schematic representation is shown displaying the aims of the study and the source of data used to answer each research question.

*Abbreviations:*P0.1*ref* = reference airway occlusion pressure measured at the airway pressure, P0.1*vent* = P0.1 displayed by the ventilator

Figure 3 P0.1 as a measure of respiratory drive and inspiratory effort per minute

A) Schematic representation of the relationship between respiratory drive and inspiratory effort in an intubated patient and difference between the reference P0.1 (measured at the airway pressure close to the Y-piece) and the ventilator P0.1 (displayed on the screen of the ventilator). Panels B) and C) display the correlation between P0.1*vent* and alternative measures of respiratory drive (rate of increase in electrical activity of the diaphragm and muscular pressure respectively). Each dot corresponds to a patient or healthy subject in a

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clinical condition. Regression lines are drawn in red and shaded grey areas correspond to 95% CI. B) Corresponds to *RegAIN* study (N= 49 tracings in 13 patients, between-subjects R^2 = 0.39, within-subjects R^2 = 0.75) and in C) data from *PCV/APRV* and *RegAIN* studies are pooled together (N= 69 tracings in 22 patients, between-subjects R^2 = 0.38, within-subjects R^2 = 0.90). D), E), F) and G) show discriminative accuracy of P0.1*ref* and P0.1vent to detect potentially injurious inspiratory effort per minute (≤ 50 $cmH_2O \cdot s \cdot min^{-1}$ and ≥200 $cmH_2O \cdot s \cdot min^{-1}$). D) and E) Validation dataset (*MYOTRAUMA* study) for P0.1ref, AUCROC [CI 95%] 0.97 [0.88-1.00] for low effort per minute and 0.91 [0.79-0.98]. F) and G) Derivation dataset *(APRV/PCV* study*)* for P0.1vent (Evita-XL) AUCROC [CI 95%] 0.92 [0.76-0.99] for low effort per minute and 0.81 [0.76-0.99]. H) Relationship between effort per minute and P0.1. Each dot corresponds to a patient in a clinical condition (N=143 tracings in 37 patients). The relationship between PTP/min and P0.1*ref* is represented in purple (data from *APRV/PCV* and *MYOTRAUMA* studies) regression line is continuous and shaded grey area correspond to 95% CI (between-patient R^2 = 0.67, within-patient R^2 =0.86). The relationship between PTP/min and P0.1*vent* is represented in purple regression line is dashed for data corresponding to *APRV/PCV* study (patients connected to Evita-XL) and dotted for data corresponding to *RegAIN* (healthy subjects connected to Servo-i) shaded grey area correspond to 95% CI (between-patients R^2=0.25, within-patients R^2=0.85 for patients and between-subjects R^2=0.47, and within-subjects R^2=0.84 for healthy subjects).

Abbreviations: P0.1*ref* = reference airway occlusion pressure measured at the airway pressure, P0.1*vent* = P0.1 displayed by the ventilator, AUCROC = area under the receiver operating characteristics curve, PTP/min = esophageal pressure-time product per minute, EAdipeak/Δt = rate of increase in electrical activity of the diaphragm calculated as the ratio of the maximal electrical activity of the diaphragm (EAdipeak) over time from initial increase

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in first EAdipeak, Pmus/Δt = rate of increase in muscular pressure (Pmus) calculated as the ratio of Pmus over time from initial increase to peak Pmus.

Figure 4 Bland and Altman plots showing accuracy and precision of P0.1*vent* compared to P0.1*ref* in the bench simulation study and in patients.

The difference between P0.1*vent* and the corresponding P0.1*ref* is plotted against the average of the two variables for each simulation. Black horizontal continuous line represents mean bias and dashed lines upper and lower limits of agreement. Orange and green dots represent simulations without and with intrinsic PEEP (auto-PEEP) respectively. Regression line for the difference between P0.1*vent* and P0.1*ref* across the range of P0.1 values are plotted with CI 95% for simulations with and without PEEPi. The same simulated inspiratory effort (linear decay in Pmus) and lung model were run with each ventilator in the bench study: A) Evita-XL (Dräger), B) Puritan-Bennett 840 (Covidien), C) Engström (GE Healthcare), D) Servo-u (Getinge). E) Data from the *EFFORT* study in which Puritan-Benett-840 was used and F) data from *APRV/BIPAP* study in which Evita-XL was used

Abbreviations: P0.1 = airway occlusion pressure, P0.1*vent* = P0.1 displayed by the ventilator, P0.1*ref* = reference P0.1 measured at the airway pressure, PEEPi = intrinsic positive end-expiratory pressure. Pmus = muscular pressure; PB-840 = Puritan-Benett-840.

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Table 1. Clinical characteristics of healthy subjects and patients

	Healthy subjects	Patients		
	from ReGAIN study	*Derivation* dataset (from APRV/PCV study)	*Validation* dataset (from MYOTRAUMA study)	Additional data to test accuracy of Putittan-Benett-840 in patients (from EFFORT study)
Number of patients	13	11	15	21
Number of tracings	49	28	46	42
Tracings per patient, median (min - max)	4 (2 - 4)	3 (1 – 3)	3 (1 – 6)	2
Age, years mean (SD)	25 (4)	55 (11)	54 (19)	64 (8)
Sex, n female (%)	0 (0)	3 (27)	7 (47)	4 (19)
Diagnosis, n (%)				
Pneumonia	-	2 (18)	2 (15)	0 (0)
Non-pulmonary sepsis	-	4 (36)	3 (20)	0 (0)
Postoperative (non cardiac)	-	0 (9)	5 (33)	0 (0)
Respiratory failure - other	-	4 (36)	5 (33)	0 (0)
Heart failure	-	1 (9)	0 (0)	0 (0)
Postoperative cardiac surgery	-	0 (0)	0 (0)	21 (100)
Arterial gas				
PaO_2/FiO_2 mmHg mean (SD)	-	218.1 (68.7)	228.8 (91.8)	303.7 (101.5)
PaO_2, mmHg mean (SD)	-	99 (28)	96 (33)	155 (47)
$PaCO_2$, mmHg mean (SD)	-	49 (11)	42 (7)	41 (7)
pH	-	7.38 (0.06)	7.41 (0.05)	7.35 (0.06)
Sedation				
Sedation-Agitation score	-	2 [2,3]	2 [1,3]	4 [3,4]
Use of continuous sedation, n (%)	-	13 (46)	N/A	0 (0)
Use of continuous opioids	-	9 (32)	N/A	0 (0)
Previous use of continuous NMBA	-	N/A	4 (8)	0 (0)
Ventilation mode, n (%)				
PC - CMV		10 (36)	15 (33)	0 (0)
PC - SIMV		10 (36)	0 (0)	0 (0)
PC – IMV		8 (29)	0 (0)	0 (0)
PS	49 (100)	0 (0)	31 (67)	21 (50)
CPAP 0		0 (0)	0 (0)	21 (50)

List of abbreviations: NMBA: neuromuscular blocking agents, PC – CMV: Pressure assist-control, PC – SIMV: Pressure control spontaneous intermittent mandatory ventilation, PC – IMV: Pressure control intermittent mandatory ventilation, PS: Pressure support, CPAP 0: spontaneous breathing with no pressure. N/A data not available.

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Table 2. Breathing effort and respiratory drive in healthy subjects, patients and bench simulation.

	Healthy subjects (from RegAIN study) ‡‡	Patients			Bench simulation‡‡
		Derivation dataset (from APRV/PCV study) ‡‡	*Validation* dataset (from MYOTRAUMA study)	Additional data to test accuracy of Puritan-Benett-840 in patients (from EFFORT study)	
Respiratory drive and effort					
P0.1*vent* median (IQR), cmH_2O*	0.7 (0.6,1.0)	1.9 (0.6,3.2)	-	3.5 (1.7,5.3)	1.7 (1.0,3.1)
P0.1*vent* min-max, cmH_2O*	0.2 - 2.7	0.1 - 5.5	-	0.1 - 7.5	0 - 10.7
P0.1*ref* median (IQR), cmH_2O†	-	2.0 (1.3,2.8)	3.2 (1.8,4.6)	3.0 (1.7,4.4)	1.8 (0.8,3.7)
P0.1*ref* min-max, cmH_2O†	-	0.3 - 3.9	0.0 – 12.0	0.5 – 7.0	0.1 – 10.5
EAdipeak median (IQR), μV‡	12 (7, 16)	-	-	-	-
EAdipeak/Δt median (IQR), $\mu V \cdot s^{-1}$‡	7.8 (5.7,11.3)	-	-	-	-
Pmus median (IQR), cmH_2O §	10.0 (7.2,13.2)	8.8 (6.0,14.2)	-	-	-
Pmus/Δt median (IQR), $cmH_2O \cdot s^{-1}$§	6.7 (4.0,8.6)	11.7 (8.3,25.4)	-	-	-
PTP/br median (IQR), $cmH_2O \cdot s$	9.6 (5.7,15.5)	5.8 (3.5,8.1)	6.6 (3.2,10.0)	-	-
PTP/min median (IQR), $cmH_2O \cdot s \cdot min^{-1}$	120.4 (80.1,200.8)	103.6 (42.3,165.0)	137.7 (69.3,206.1)	-	-
Mechanics					
Presence of auto-PEEP n (%)ll	-	24 (57)	13 (28)	22 (52)	147 (48)
PEEPi value median (IQR), cmH_2O††	-	1.5 (1.3,2.5)	1.6 (1.2,5.2)	1.9 (1.4,2.3)	4.4 (3.0,5.9)

Abbreviations: P0.1vent: airway occlusion pressure (P0.1) displayed on the ventilator screen; P0.1*ref*: reference P0.1 measured from airway pressure recording; PTP/br: pressure-time product of the esophagus per breath; PTP/min: pressure-time product of the esophagus per minute; PEEPi: intrinsic positive end-expiratory pressure * P0.1vent not available in MYOTRAUMA study. †P0.1*ref* not measured in healthy subjects, given lack of occlusion. ‡EAdi derived parameters only measured in healthy subjects. §Pmus/Δt measured in healthy subjects and derivation dataset to compare with P0.1*vent* with an alternative measure of drive. ll In the bench simulation auto-PEEP was defined as the presence of instrinsic positive end-expiratory pressure (PEEPi) ≥ 0.5 cmH_2O, in the patients it was defined as the presence of PEEPi ≥ 1.0 cmH_2O. ††Considering tracings with auto-PEEP.‡‡ For each dataset, P0.1vent was displayed by the following ventilators: In RegAIN Servo-i (Getinge), in APRV/PCV Evita-XL (Dräger), in EFFORT Puritan-Bennett-840 (Medtronic) and in the bench simulation Servo-i, Servo-u (Getinge), Ëngstrom (GE Healthcare), Carescape R860 (GE Healthcare), Puritan-Bennett 840, and Evita-XL.

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Table 3 – Diagnostic performance of threshold values of P0.1 measured at the airway pressure (P0.1*ref*) and P0.1 displayed by the ventilator (P0.1*vent*) to detect potentially injurious effort.

	PTP/min ($cmH_2O \cdot s \cdot min^{-1}$)	AUC ROC [CI 95%]	P0.1 (cmH_2O)	Sensitivity	Specificity	Diagnostic accuracy	+LR	-LR	PPV	NPV
P0.1ref - high effort	**200**									
Validation dataset		**0.91 [0.79 - 0.98]**								
Published threshold			3.5	0.80	0.77	0.78	3.54	0.26	0.63	0.89
Best threshold*			2.8	1.00	0.68	0.78	3.10	0.32	0.60	1.00
P0.1ref - high effort	**300**									
Derivation dataset		**0.92 [0.76 - 0.99]**								
Best threshold*			3.9	1.00	0.92	0.93	12.5	0.00	0.50	1.00
Validation dataset		**0.96 [0.85 - 0.99]**								
Best threshold in derivation			3.9	1.00	0.80	0.83	5.00	0.00	0.43	1.00
Best threshold*			4.7	1.00	0.88	0.89	8.33	0.00	0.55	1.00
P0.1ref - low effort	**50**									
Derivation dataset		**0.97 [0.82 - 1.00]**								
Best threshold*			1.1	1.00	0.92	0.93	12.00	0.00	0.67	1.00
Validation dataset		**0.97 [0.88 - 1.00]**								
Best threshold*			1.1	1.00	0.92	0.93	13.00	0.00	0.73	1.00
P0.1vent† - high effort	**200**									
Derivation		**0.81**								

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dataset		**[0.63 - 0.94]**								
Published threshold P0.1ref			3.5	0.67	0.86	0.82	4.89	0.39	0.57	0.91
Best threshold*			4.0	0.67	0.91	0.86	7.33	0.37	0.67	0.91
P0.1vent† - low effort	**50**									
Derivation dataset		**0.92 [0.76 - 0.99]**								
Best threshold P0.1ref			1.1	0.75	0.95	0.89	9.00	0.27	0.6	0.96
Best threshold*			1.3	1.00	0.88	0.89	8.00	0.12	1.00	1.00

List of abbreviations and equations: P0.1 = airway occlusion pressure; P0.1*ref* = reference P0.1 measured at the airway pressure; P0.1*vent* = P0.1 displayed by the ventilator; PTP/min = pressure-time product per minute; AUCROC = area under the receiver operating characteristics curve; TP = true positive; TN = true negative; FP = false positive; FN = false negative. Sensitivity = TP/(TP+FN); Specificity = TN/(TN+FP); Diagnostic accuracy = (TP+TN)/(TP+TN+FP+FN); +LR = positive likelihood ratio = Sensitivity/(1-Specificity); -LR = negative likelihood ratio = (1-Sensitivity)/Specificity; PPV = TP/(TP+FP); NPV = TN/(TN+FN).

*Best threshold corresponding to the highest Youden index (Sensitivity + Specificity – 1)

Validation dataset corresponds to randomly selected tracings from MYOTRAUMA study and *derivation* dataset to selected tracings from APRV/PCV study (end-expiratory occlusion in the airway pressure tracing).

† Evita-XL was used in the PCV/APRV dataset

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Table 4 Agreement between airway occlusion pressure displayed by each ventilator (P0.1*vent*) and reference method to measure airway occlusion pressure (P0.1*ref*).

Ventilator	N§	Type of decay in Pmus	Auto-PEEP ‡, n (%)	Bias [95% CI], cmH_2O	Limits of agreement†, cmH_2O	Proportional Bias * [95% CI], %	Proportional limits of agreement*, %
BENCH SIMULATION							
Evita-XL	48	Linear	24 (50)	0.3 [0.2,0.3]	-0.3, 0.8		
Puritan Benett 840	48	Linear	22 (46)	0.1 [0.1,0.2]	-0.2, 0.4		
GE Engström	45	Linear	21 (47)	0.3 [0.1,0.5]	-1.0, 1.6		
GE Carescape R860	32	Non-linear	14 (44)	-0.1 [-0.4,0.1]	-1.4, 1.2		
Servo-i							
Sensitive trigger	48	Linear	23 (48)	-0.3 [-0.6,-0.1]	-2.2, 1.5	-5.2 [-15.7, 5.2]	-75.8, 65.3
Sensitive trigger	36	Non-linear	18 (50)	-1.1 [-1.5,-0.7]	-3.6, 1.4	-33.4 [-43.5, -23.3]	-91.9, 25.1
Servo-u							
Sensitive trigger	48	Linear	24 (50)	-0.4 [-0.7,-0.3]	-1.8, 0.9	-13.3 [-23.1,-3.4]	-79.6, 53.0
Low sensitive pressure trigger	23	Linear	0 (0)	-0.1 [-0.2,0.0]	-0.5, 0.3	-	-
PATIENTS†							
Evita-XL	28	-	13 (46)	0.0 [-0.3, 0.3]	-1.6, 1.6	-	-
Puritan Benett 840	42	-	22 (52)	0.3 [0.0, 0.5]	-1.2, 1.8	-	-

List of abbreviations: N = number of simulations (bench) and tracings (patients) included, Auto-PEEP = intrinsic positive end-expiratory pressure, Pmus = muscular pressure

*Proportional bias and limits of agreement was only calculated for experiments where an increase in variability of the difference between P0.1 displayed by the ventilator (P0.1*vent*) and the reference P0.1 measured from airway pressure recording (P0.1ref), was observed as the magnitude of the measurement increased. †Within patient repeatability limits were calculated to account for repeated measures in patients using linear mixed-effects model. ‡In the bench simulation auto-PEEP was defined as the presence of instrinsic positive end-expiratory pressure (PEEPi) ≥ 0.5 cmH_2O, in the patients it was defined as the presence of PEEPi ≥ 1.0 cmH_2O. § As detailed in the ES, number of simulations performed for each ventilator with a sensitive trigger using a linear decay in Pmus were 48 and with a non-linear decay of Pmus were 36. 24 simulations were performed in the Servo-u using a less sensitive pressure trigger. Some simulations were discarded due to ineffective efforts and technical issues.

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Figure 1

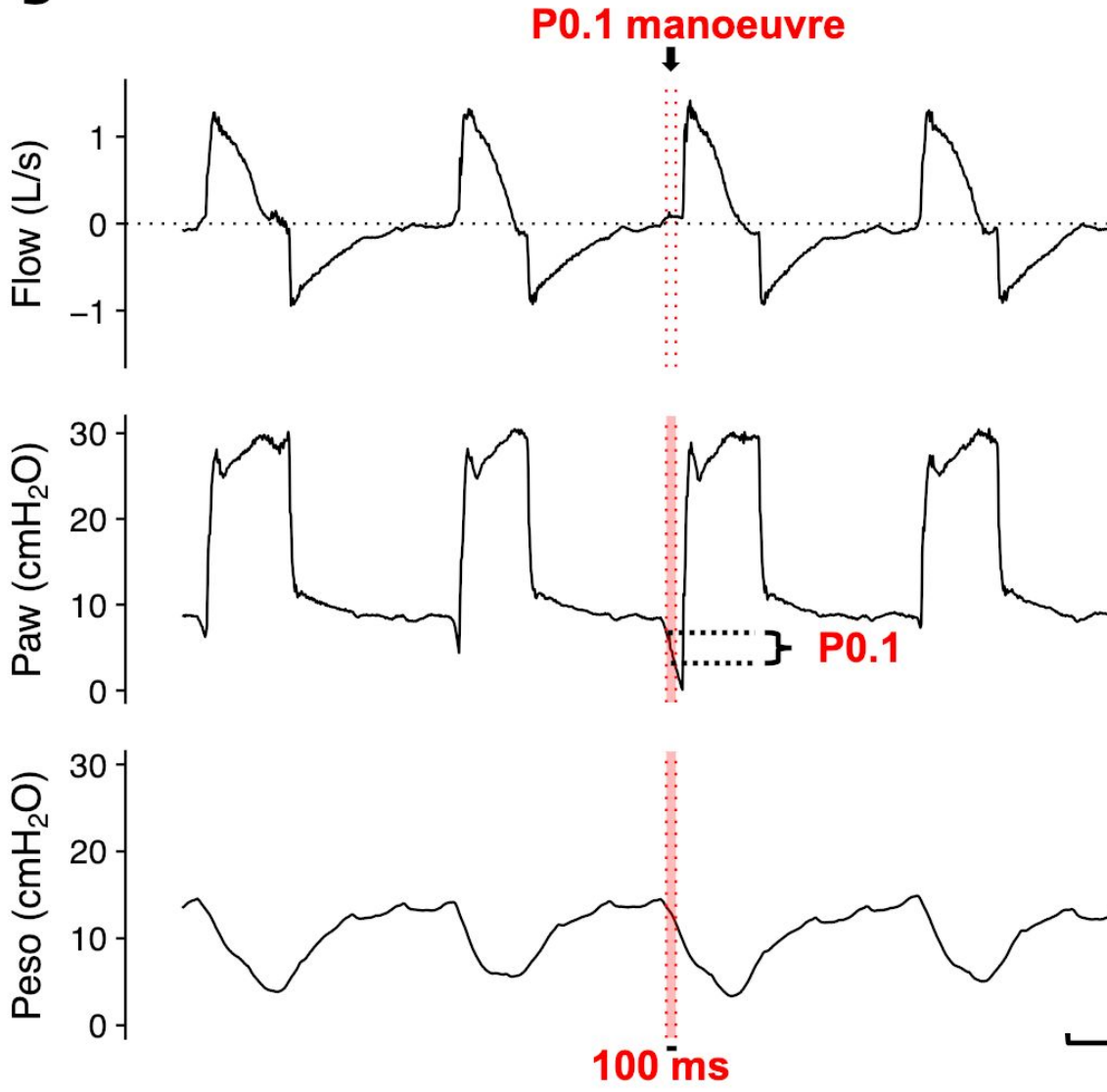

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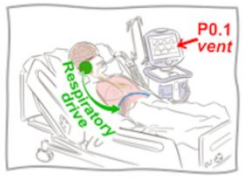
Figure 2

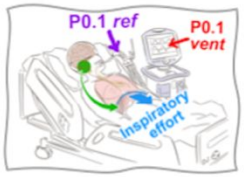
AIM 1



Validation of P0.1 displayed by the ventilator as a measure of respiratory drive

1. Physiologic study in healthy subjects *(RegAIN)*
2. Clinical study in patients *(PCV/APRV)*

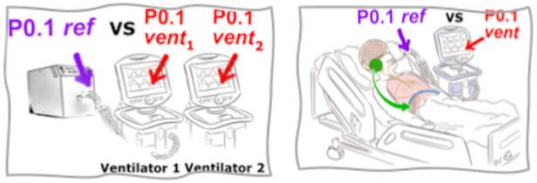
AIM 2



a) Correlation between P0.1 and inspiratory effort
b) Validation of P0.1 to detect potentially excessive and low inspiratory effort

1. Clinical studies in patients:
    1. DERIVATION DATASET *(PCV/APRV)*
    2. VALIDATION DATASET *(MYOTRAUMA)*

AIM 3



Comparison of P0.1 displayed by different ventilators to a reference technique to measure P0.1

1. Bench simulation:
    1. Evita-XL, PB-840, Servo-i, Servo-u, Engström, Carescape R860
2. Clinical studies in patients:
    1. *PCV/APRV:* Evita-XL
    2. *EFFORT:* PB 840

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Figure 3

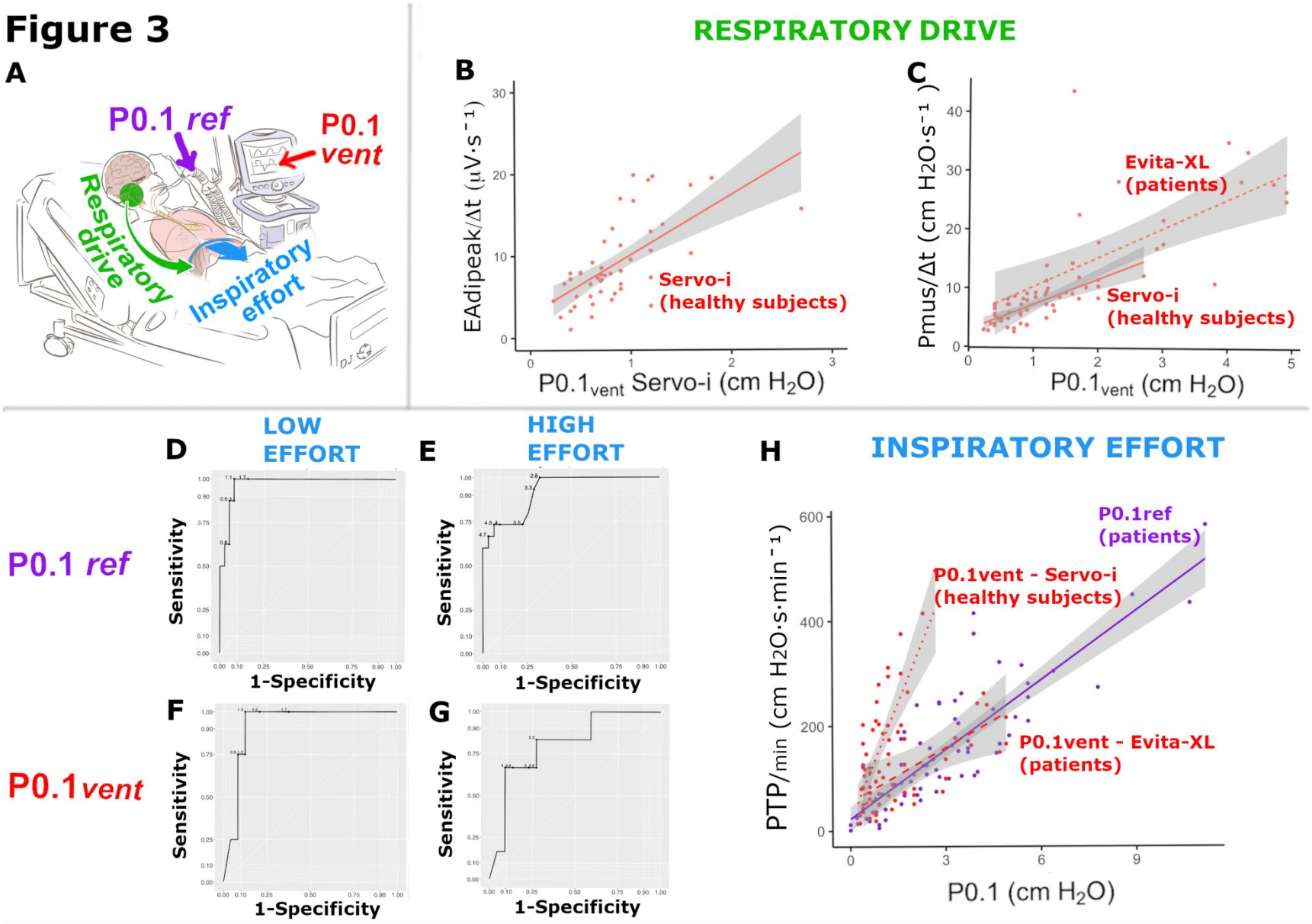

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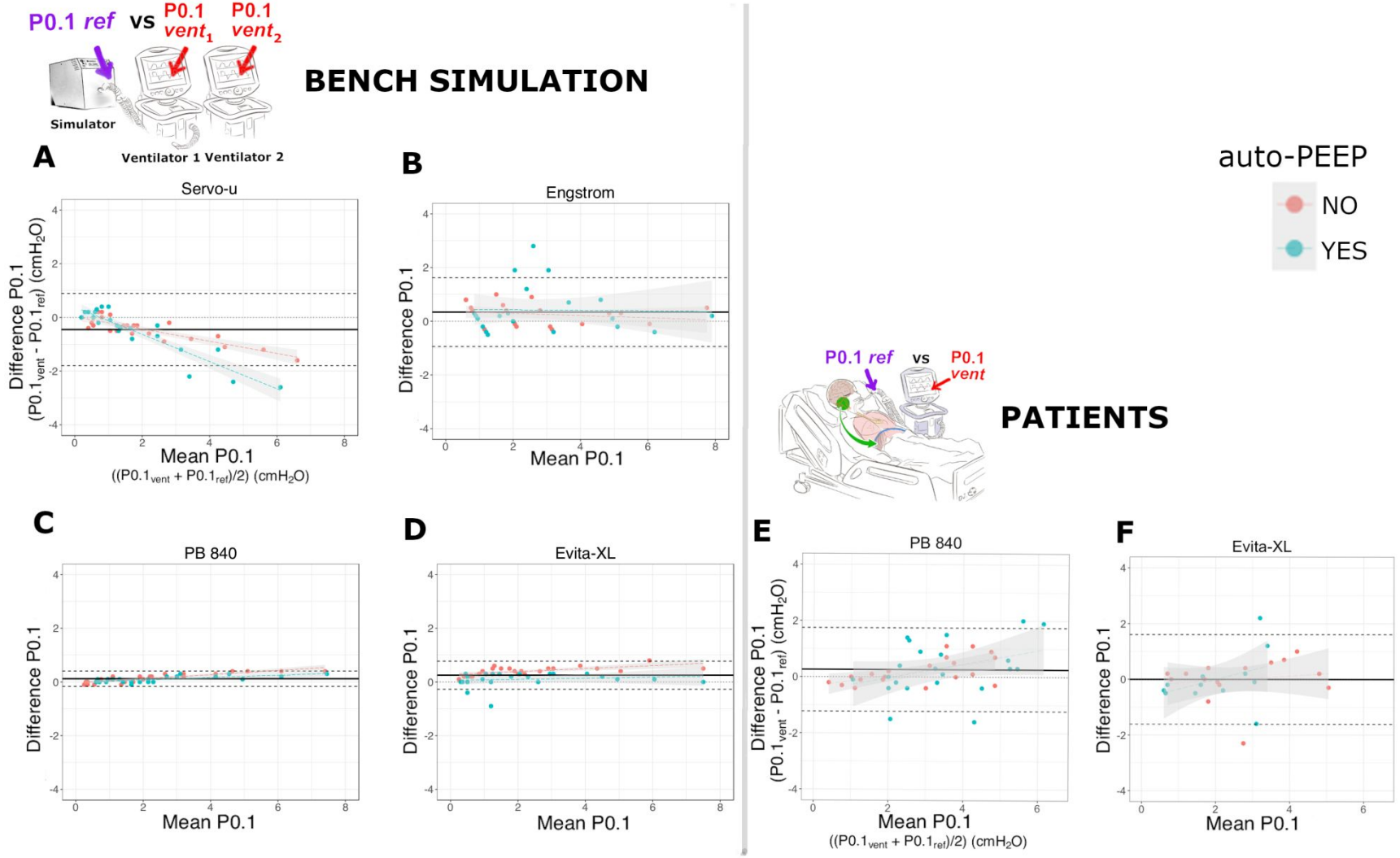
Figure 4



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Airway Occlusion Pressure as an Estimate of Respiratory Drive and Inspiratory Effort During Assisted Ventilation

Online Data Supplement

Irene Telias, Detajin Junhasavasdikul, Nuttapol Rittayamai, Lise Piquilloud, Lu Chen, Niall D Ferguson, Ewan C Goligher, Laurent Brochard

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Diaphragm Injury and Dysfunction During Mechanical Ventilation (MYOTRAUMA) (Clinicaltrials.gov # NCT03108118) **5**

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Acceptable Range of Inspiratory Effort During Mechanical Ventilation (EFFORT) (Clinicaltrials.gov #NCT02838524) **6**

Eligibility 6
Data collection 6
Procedures 6

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Human data

Table E1 – Design of each study included in the present analysis

Study	APRV/BIPAP[1]	MYOTRAUMA[2]	EFFORT[3]	RegAIN[4]
Objectives	• To validate P0.1 *vent* (Evita-XL) as a measure of respiratory drive • To determine the ability of P0.1*ref* to detect potentially injurious respiratory effort (derivation dataset) • To determine the ability of P0.1*vent* (Evita-XL) to detect potentially injurious respiratory effort (derivation dataset) • To examine the accuracy and precision of P0.1*vent* (Evita-XL) compared to P0.1*ref* in patients	• To validate the ability of P0.1*ref* to detect potentially injurious respiratory effort (validation dataset)	• To examine the accuracy and precision of P0.1*vent* (PB-840) compared to P0.1*ref* in patients	• To validate P0.1 *vent* (Servo-i) as a measure of respiratory drive • To explore the correlation between P0.1*vent* and inspiratory effort in healthy subjects
Setting	2 medical-surgical ICUs	2 medical-surgical ICUs	1 cardiovascular ICU	A physiology laboratory
Inclusion	Patients on invasive MV breathing spontaneously on PCV or PS ≥ 10 cmH_2O.	Patients on invasive MV for less than 36hs and expected to be intubated for ≥ 7 days for acute brain injury, ARDS, septic shock or pneumonia	Patients on invasive MV after scheduled uncomplicated cardiac surgery	Healthy non-obese males between 18 and 35 years old with normal respiratory function confirmed by lung function tests.
Exclusion	Hemodynamic instability, PEEP ≥ 12 cmH2O, FiO2 > 0.6, 7.30 > pH < 7.55, chronic neuromuscular disease, intracranial hypertension, pregnancy, contraindication for nasogastric tube insertion.	Contraindication for nasogastric tube insertion or acute exacerbation of obstructive airways disease	Pregnancy, decompensated cardiac failure, acute coronary syndrome, or severe COPD	Contraindication for nasogastric tube insertion.
Data collection	• Flow, Paw and Peso recorded with dedicated device (Biopac systems)	• Flow and Paw recorded by the ventilator (stored in a laptop with Neurovent software). • Peso measured with a dedicated device (Neurovent) in synchrony.	• Flow, Paw recorded with dedicated device (Biopac systems)	• Flow, Paw and EAdi recorded by the ventilator (stored in a laptop with Servo-tracker software). • Peso measured with a dedicated device (Biopac systems) in synchrony
Ventilator	Evita-XL	Servo-i	PB-840	Servo-i
Procedures	• 5 min recordings in 3 modes: PCV+assist, PCV+, and APRV • Each recording, random activation of P0.1 manoeuvres every minute	• 10 min recordings once daily (on clinical ventilator mode and settings). • Each recording, random activation of end-expiratory occlusion manoeuvres on the ventilator (every 15 sec)	• 5 min recordings in 2 modes: PS 5 cmH2O with PEEP 5 cmH_2O and CPAP 0 cmH_2O. • Each recording, random activation of P0.1 manoeuvres every minute.	• Ventilation through tight orofacial mask • 10 min recordings in 4 conditions: low- and high-pressure support (PS) with and without an added resistance*

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Parameters	PTP/br, PTP/min, P0.1*vent*, P0.1*ref*	PTP/br, PTP/min, P0.1*ref*	P0.1*vent*, P0.1*ref*	PTP/br, PTP/min, EAdi, P0.1*vent*

Complete name of each study and registration number at clinicaltrials.gov: [1]APRV/BIPAP: APRV/BIPAP With Spontaneous Breathing on Lung Protection (# NCT02071277), [2]MYOTRAUMA: Diaphragm Injury and Dysfunction During Mechanical Ventilation (#NCT03108118), [3]EFFORT: Acceptable Range of Inspiratory Effort During Mechanical Ventilation (#NCT02838524), [4]RegAIN: Effects of Abnormal Respiratory Mechanics and Assisted Mechanical Ventilation on Neuro-regulation of Respiration (Clinicaltrials.gov #NCT01818219)
*Added resistance: 20 $cmH_2O \cdot l^{-1} \cdot s^{-1}$. Without resistance: low PS 2 cmH_2O, high PS 7 cmH_2O. With resistance: low PS 7 cmH_2O, high PS 14 cmH_2O.

List of abbreviations: PCV: pressure assist-control ventilation; PS: pressure support ventilation; PEEP: positive end-expiratory pressure, Paw: airway pressure; Peso: esophageal pressure; EAdi: electrical activity of the diaphragm; PCV+assist: pressure controlled continuous mandatory ventilation (fully synchronized mode); PCV+: pressure controlled synchronized intermittent mandatory ventilation (partially synchronized mode); APRV: pressure controlled intermittent mandatory ventilation (non-synchronized mode); PTP/br: pressure-time product per breath of the esophagus; PTP/min: pressure-time product per minute of the esophagus; P0.1*ref*: reference method to measure airway-occlusion pressure; P0.1*vent*: airway occlusion pressure displayed by the ventilator; ARDS: acute respiratory distress syndrome; CPAP: continuous positive airway pressure; COPD: chronic obstructive pulmonary disease.

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Details of the human data

This is an ancillary post hoc analysis of four clinical studies (Table E1) assessing respiratory drive and inspiratory effort during assisted mechanical ventilation. Additional details of each study relevant to the present analysis are provided in this supplement.

APRV/BIPAP With Spontaneous Breathing on Lung Protection (APRV/BIPAP) - (Clinicaltrial.gov # NCT02071277)

The study was conducted in two medical-surgical intensive care units in Toronto, Canada, at St. Michael´s Hospital and Mount Sinai Hospital. Details and main results of this study have been published (1).

Eligibility

Included patients breathing spontaneously under invasive mechanical ventilation, on pressure assist-control ventilation (PCV) or pressure support ventilation (PS) of at least 10 cmH_2O.

Data collection

A Fleisch No.2 pneumotachograph and an additional port for airway pressure (Paw) were placed between the Y-piece and the tip of the endotracheal tube, connected to differential pressure transducers (TSD160series: Biopac systems, Goleta, CA, USA). Paw, flow and esophageal pressure (Peso) were processed with an analogue-digital converter (MP150; Biopac systems, Goleta, CA, USA), sampled at 100 Hz and stored in a laptop computer.

Procedures

Evita-XL or V500 (Dräger, Lübeck, Germany) ventilators were used but only data using Evita-XL was selected. Patients were placed in three modes of ventilation for 20 minutes each (PCV+assist, PCV+, and APRV) keeping inspiratory pressure, PEEP, set respiratory rate, FiO_2 and inspiratory time unchanged between conditions. During the last 5 minutes signals were recorded, a P0.1 manoeuver was activated on the ventilator every minute, and the value displayed on the ventilator screen (P0.1*vent*) was recorded. Each period of recording (one mode of ventilation) was considered an observation (tracing). Only tracings with at least 3 P0.1 manoeuvers that were evident on Paw and flow tracings evaluated offline were included for analysis.

Diaphragm Injury and Dysfunction During Mechanical Ventilation (MYOTRAUMA) (Clinicaltrials.gov # NCT03108118)

The study was conducted in two medical-surgical intensive care units of the University Health Network in Toronto, Canada. Preliminary results were published as an abstract (2).

Eligibility

Included patients were intubated for acute brain injury, acute respiratory distress syndrome, septic shock or pneumonia for less than 36 hours and were expected to be intubated for at least one week. They were excluded if they had any contraindication for esophageal catheterization or acute exacerbation of obstructive airways disease.

Data collection

Airway pressure (Paw) and flow measured by the ventilator were recorded at a sampling frequency of 62.5 Hz by a laptop computer connected to the ventilator using dedicated software (Neurovent Inc., Toronto, Canada). Esophageal pressure was measured with a pressure transducer attached to the Neurovent monitoring system in synchrony with the other signals and stored in a laptop computer. Linear interpolation was used for analysis.

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Procedures

Once daily, five to ten minutes recordings were performed. Ventilator mode and settings were unchanged and several single-breath end-expiratory occlusions were performed every 15-20 seconds by means of activation of an end-expiratory occlusion manoeuvre on the ventilator. No information regarding P0.1*vent* was recorded. Each period of recording was considered an observation (tracing). Tracings were selected at random including recordings for more than one day for each patient.

Acceptable Range of Inspiratory Effort During Mechanical Ventilation (EFFORT) (Clinicaltrials.gov #NCT02838524)

The study was conducted in a Cardiovascular Intensive Care Unit (CVICU) at St. Michael´s Hospital in Toronto, Canada. Preliminary results were published as an abstract (3).

Eligibility

Intubated adult (more than 17 years old) patients were included after scheduled cardiac surgery if they were deemed ready to undergo a trial of spontaneous breathing according to the local ICU protocol. Patients were excluded if they were pregnant, had decompensated cardiac failure, acute coronary syndrome, or severe chronic obstructive pulmonary disease.

Data collection

A variable orifice type flow sensor (Hamilton Medical AG, Bonaduz, Switzerland) and an additional port for Paw were placed between the Y-piece and the tip of the endotracheal tube, connected through special tubing to differential pressure transducers (TSD160series: Biopac systems, Goleta, CA, USA). Paw and flow signals were processed with an analogue-digital converter (MP150; Biopac systems, Goleta, CA, USA), sampled at 200 Hz and stored in a laptop computer for off-line analysis.

Procedures

After cardiovascular surgery, when the patient was awake, he or she was placed on three breathing modalities for five minutes each in random order: pressure support of 5 cmH_2O and PEEP of 5 cmH_2O (P5), continuous positive airway pressure of 0 cmH_2O (CPAP0), and T-piece. Puritan-Bennett 840 (Medtronic) ventilator was used for all patients.

During each five-minute period respiratory signals were recorded, a P0.1 manoeuvre was activated on the ventilator every minute during P5 and CPAP0, and the value displayed on the ventilator screen (P0.1vent) was recorded. Each period of recording (one mode of ventilation) was considered an observation (tracing). The first 21 included patients were selected for the present analysis including the first 3 P0.1 manoeuvres in each condition.

Effects of Abnormal Respiratory Mechanics and Assisted Mechanical Ventilation on Neuro-regulation of Respiration (ReGAIN) (Clinicaltrials.gov #NCT01818219)

This study was conducted in a physiology laboratory corresponding to the Department of Medical Intensive Care of the University Hospital of Angers, France.

Eligibility

Healthy non-obese males (body mass index ≤ 30 kg/m^2) between 18 and 35 years old without contraindication for nasogastric tube insertion were included. Normal respiratory function was confirmed by lung function tests.

Data collection

A nasogastric tube equipped with electrodes and an esophageal balloon (Neurovent Research Inc Toronto, Canada) was inserted through the nose to record EAdi and Peso.

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Recordings of Paw, flow, and Eadi were acquired with the Servo-i® ventilator (Getinge group) sampled at 100Hz, recorded and stored in a laptop computer with a specific software (Servo-tracker 4.2, Getinge group). Peso was recorded in synchrony with the other signals using a pressure transducer connected to an analog-to-digital converter (Biopac systems, Goleta, CA, USA) and stored in a computer.

Procedures

Subjects received ventilatory support (Servo-i, Getinge group) using a tight orofacial mask during four ventilatory conditions: low- and high-pressure support (PS) with and without an added resistance (20 $cmH_2O \cdot L^{-1} \cdot s^{-1}$). Without the added resistance low and high PS were set at 2 and 7 cmH_2O respectively and with the added resistance at 7 and 14 cmH_2O respectively. Each condition was maintained during 10 min, recording the last 5 minutes. P0.1*vent* was recorded from the ventilator screen in each condition. Given that no end-expiratory occlusion was performed, there was no P0.1*ref* measurement. All recorded tracings were included.

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Selection of thresholds for excessive inspiratory effort

Risk of injury due to excessive inspiratory effort depends on the magnitude, timing and duration of breathing effort as well as patient characteristics and ventilator settings. Load induced diaphragm injury and dysfunction is present in animal models and humans that breath with a load closed to fatiguing thresholds (4, 5). Reaching these thresholds might also have adverse consequences to the lung and distant organs in the form of patient self-inflicted lung injury (6) and decreased oxygen delivery. At the end of a failed spontaneous breathing trial (SBT) patients are close to their fatiguing thresholds resulting in resumption of ventilatory assistance by clinicians (7). On the other hand, inspiratory effort during a successful SBT is lower and seems to be not acutely injurious since patients are able to sustain ventilation at these levels after extubation (8). Therefore, a safe, non-fatiguing, and potentially non-injurious upper threshold is represented by the upper limit of breathing effort during successful SBTs.

There are few physiological studies measuring inspiratory effort during SBT reviewed in Table E2 which show that inspiratory effort measured using pressure-time product varies according to technical details and different patient populations. The data was extracted from papers included in the systematic review and meta-analsysis performed by our study group in which values of breathing effort during T-piece were reported using pressure-time product (8). Additionally, risk of injury regardless of the magnitude of breathing effort might varies according to patient´s susceptibility, being higher in those with systemic inflammation and worse lung injury as shown by experimental data (9, 10). On the other hand, patients with adequate respiratory muscle function or special populations that usually perform stronger breathing efforts at rest (e.g. morbidly obese subjects) might be able to tolerate higher amount of effort without risk. Therefore, we selected two thresholds to test the accuracy of P0.1ref for excessive inspiratory effort based on the reviewed articles: 200 and 300 cmH2O·s·min^{-1}. Given the lower number of observations available for P0.1vent and only 2 tracings having and inspiratory effort higher than 300 cmH2O·s·min^{-1}, we opted to test only one threshold selecting 200 cmH2O·s·min^{-1}.

Table E2 - Summary of studies reporting inspiratory effort during spontaneous breathing trials

Author, year	Number of patients	Subgroup of patients	Inspiratory effort PTP ($cmH_2O \cdot s \cdot min^{-1}$) Mean (SD) or Median [IQR]	Threshold for excessive inspiratory effort PTP ($cmH_2O \cdot s \cdot min^{-1}$)	Comments
Jubran A, 1997 (11)	17	Success of SBT on T-piece (COPD patients)	180 (22)	200	Corresponds to a TTI of 0.06 (0.01) Estimated CCW. Excludes auto-PEEP.
Koh Y, 2000 (12)	8	Success of SBT on T-piece	155 (47)	200	Technical details missing
Nathan SD, 1993 (13)	7	Success of SBT on T-piece	149 (45)	200	Includes PTP due to auto-PEEP. How CCW was measured not specified
Cabello B, 2010 (14)	14	Failure of SBT on T-piece	292 [238, 512]		
		Most success of SBT on PSV (11/14 patients)	128 [28,299]	300	Estimated CCW, included corrected auto-PEEP (using Pga)
Ishaaya AM, 1995 (15)	8	Success of SBT on T-piece	200 (70)	300	Estimated CCW, included auto-PEEP. Absolute values estimated from figure.

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Sasson C, 1991 (16)	10	Success of SBT on T-piece	245 (64)	300	Estimated CCW, included auto-PEEP. Absolute values estimated from figure
Mehta S, 2000 (17)	20	Success of SBT on T-piece	240 (103)	350	Technical details not provided. Large variability in effort.
Mahul M, 2016 (18)	17	Success of SBT on T-piece (morbidly obese patients)	439 (152)	600	Special population: morbidly obese patients. Included auto-PEEP.

List of abbreviations: PTP: pressure-time product of the respiratory muscles, SD: standard deviation, IQR: interquartile range, TTI: tension-time index, SBT: spontaneous breathing trial, CCW: chest-wall compliance.

Relationship between P0.1 and respiratory drive and effort in healthy subjects vs patients

Validation of P0.1*vent* as a measure of respiratory drive in healthy subjects was performed by means of comparing P0.1*vent* with two alternative measures of respiratory drive, the rate of increase in muscular pressure (Pmus/Δt) and the rate of increase in electrical activity of the diaphragm (EAdipeak/Δt). Correlation between Pmus/Δt and P0.1*vent* was also used in patients to validate the use of P0.1*vent* as a measure of respiratory drive.

Both P0.1*vent* and Pmus/Δt express a rate of change in pressure. A significant positive correlation between these two parameters is a way to independently validate P0.1*vent* as a measure of respiratory drive because both are derived from different biological signals (airway pressure vs muscular pressure), were measured by independent systems (the ventilator vs an investigator using specific equipment including esophageal manometry) and the rate of change was calculated over a different time period (100 msec vs time from initial increase to peak muscular pressure). Therefore, technical errors in the measurement of P0.1*vent* would have resulted in a lack of correlation between both parameters invalidating the use of P0.1*vent* as a measure of drive.

Interestingly, the slope of the relationship between P0.1*vent* and Pmus/Δt in healthy subjects and in patients was very similar (Figure 3C) despite P0.1*vent* being measured by different ventilators. In contrast, the slope of the relationship between P0.1 (vent and ref) and inspiratory effort (PTP/min) was different between healthy subjects and patients (Figure 3H). Taken together, these findings suggest that the relationship between respiratory drive and inspiratory effort is, as expected, different between healthy subjects and critically ill patients under assisted mechanical ventilation. In patients the different degrees of neuromechanical efficiency and respiratory muscle dysfunction explain the variability between patient´s individual relationship resulting in a poorer or less efficient coupling than in healthy subjects.

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Methods

Bench study

Table E3 – Design of the bench study

Objective	• To compare the accuracy and precision of P0.1vent compared to P0.1ref across ventilators • To test the influence of auto-PEEP on accuracy and precision of P0.1vent compared to P0.1ref	• To test the influence of the shape of Pmus on accuracy and precision of P0.1vent compared to P0.1ref • To test the influence of auto-PEEP accuracy and precision of P0.1vent compared to P0.1ref	• To test the influence of trigger sensitivity on accuracy and precision of P0.1vent compared to P0.1ref in ventilators without true occlusions
Simulation	• Normal and obstructive lung physiology • 24 patterns of Pmus with linear decay • 48 simulations each ventilator	• Normal and obstructive lung physiology • 18 patterns of Pmus with non-linear decay • 36 simulations each ventilator	• Normal lung physiology • 24 patterns of Pmus with linear decay • Total 24 simulations
Ventilators	• Lack of true occlusion: o Servo-i o Servo-u • With true occlusion: o Evita-XL o PB-840 o Engström	• Lack of true occlusion: o Servo-i • With true occlusion: o R860	• Lack of true occlusion: o Servo-u
Ventilator settings	Mode: Pressure support	Mode: Pressure support	• Mode: Pressure support
Trigger sensitivity	Pressure -1 cmH_2O or flow 2l/min randomly assigned to each simulation	Pressure -1 cmH_2O or flow 2l/min randomly assigned to each simulation	Pressure -2 to -5 cmH_2O depending on Pmus (as displayed in Table E5)
Procedures	• **Servo**: 5 min recording and 3 end-expiratory occlusions. • **Other**: 5 min recording, 3 P0.1 maneouvers and 3 end-expiratory occlusions	• **Servo**: 5 min recording and 3 end-expiratory occlusions. • **R860**: 5 min recording, 3 P0.1 maneouvers and 3 end-expiratory occlusions	• **Servo**: 5 min recording and 3 end-expiratory occlusions.

List of abbreviations: Pmus: muscular pressure, P0.1: airway occlusion pressure

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Setting

This study was conducted in a physiology laboratory corresponding to the Department of Intensive Care of St. Michael´s Hospital in Toronto, Canada. Preliminary results were published as abstracts (19, 20). The ASL 5000 lung simulator (Ingmar Medical) was used. It is a digitally controlled real-time breathing computerized simulator consisting of a piston moving inside a cylinder. To control the piston's movement, a microprocessor is programmed with a script driver, which uses a mathematical model based on the equation of motion.

Lung model

Two lung models were simulated using a single-compartment model (a single value for resistance and compliance) for each: a) **Normal**: Resistance (R_{RS}) = 10 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ and Compliance (C_{RS}) = 60 $ml \cdot cmH_2O^{-1}$. b) **Obstructive** (with increased expiratory resistance to simulate intrinsic PEEP -PEEPi): Inspiratory resistance (R_{RSin}) = 10 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ Expiratory resistance (R_{RSout}) = 30 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ and C_{RS} = 60 $ml \cdot cmH_2O^{-1}$.

Patient effort model

A trapezoidal and a semi-sinusoidal inspiratory waveform were selected to simulate a linear and non-linear decay of patient´s inspiratory effort respectively. Expiration was passive. Respiratory rate was set at 12 and 20 bpm combined with the normal and obstructive lung model respectively. A total of 24 and 18 patterns of inspiratory effort were simulated using the linear and non-linear inspiratory waveforms respectively by combining the following settings: 1) maximum inspiratory pressure raging from 3 to 25 cmH_2O, 2) rise time of inspiratory waveform (%Increase i.e. % of total time spent from the start of the effort to the maximum effort) raging from 6 to 35%, 3) inspiratory hold 0% of total time, and 4) releasing time (%Release, i.e. % of total time spent from maximum effort to baseline) 20%

Linear decay (trapezoidal waveform) was used with Servo-i and Servo-u (Getinge group), Engström (GE Healthcare), Puritan Benett 840 (PB-840, Medtronic) and Evita-XL (Dräger) ventilators. Non-linear decay (semi-sinusoidal waveform) was used with Servo-i (Getinge group) and Carescape R860 (GE Healthcare) ventilators.

As a result, total of 48 and 36 combinations of lung model + patient effort simulations were performed with each ventilator when a linear, and non-linear decay of patient effort was used, respectively. See tables E4 to E7 for details on the settings.

Ventilators settings

Pressure support ventilation (PS) was 5 (normal) or 10 cmH_2O (obstructive), PEEP was 5 cmH_2O using a sensitive trigger sensitivity (flow of 2 l/min or pressure of -1 cmH_2O each simulation being randomly assigned to one type at random), cycling off criteria was 25%.

24 additional simulations with the Servo-u ventilator were done using a less sensitive pressure trigger (that still allowed to trigger a breath) resulting in a short occlusion at end-expiration. The reason for this is that Servo ventilators do not perform an end-expiratory occlusion to measure P0.1vent. These ventilators measure the decay in airway pressure (Paw) during the trigger phase assuming that the load imposed by the inspiratory valves during this phase is similar to performing a short end-expiratory occlusion. If the assumption holds true, decay in Paw should be proportional to that of the pleural pressure. However, when trigger is sensitive in modern ventilators with efficient valves (21), the assumption does not hold, specially at

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high muscular effort resulting in P0.1*vent* underestimating the drop in pleural pressure. Setting a pressure trigger and a less sensitive one result in a short end-expiratory occlusion and P0.1*vent* being therefore a better estimate of P0.1*ref* (measured during an occlusion). The trigger sensitivity chosen varied for each simulation, increasing from -2 to -5 cmH_2O.

Data collection

A variable orifice differential pressure flow sensor (Hamilton Medical) and an additional port for Paw were placed at the entrance of the simulator´s piston, connected through special tubings to differential pressure transducers (TSD160series: Biopac systems). Flow and Paw signals were processed with an analogue-digital converter (MP150; Biopac systems), sampled at 200 Hz and stored in a laptop computer for analysis (Acqknowledge 4.3, Biopac Systems).

The recording system was calibrated prior to each experiment using a 1-liter calibration syringe (Hans Rudolph, inc) for flow and a water column for pressure. Autocalibration was run for each ventilator connected to the circuit prior to each experiment and the experimental set up was systematically tested for leaks once the ventilator was connected to the simulator and recording system by measuring the lack of change in airway pressure during an end-inspiratory occlusion with passive ventilation to achieve a plateau pressure > 25 cmH2O for at least 5 seconds.

Procedures

ASL 5000 was connected to each ventilator through a disposable double limb circuit (GE Healthcare) with dimensions: 1.5 m length each limb, internal diameter 22 mm, with a compressible volume of 1140 ml and a measured compliance of 2.1 $ml \cdot cmH_2O^{-1}$. No humidification system was used.

With the ASL 5000 connected to each ventilator, each simulation was run for five minutes for stability. Then, the procedure varied according to the ventilator, given its technical differences in estimating or measuring P0.1.

Servo ventilators (Servo-i, Servo-u)

Three consecutive P0.1vent were recorded, then three end-expiratory occlusion manoeuvres were activated lasting one breath each for measuring P0.1ref and auto-PEEP offline.

Others (Ëngstrom, R860, Evita-XL, PB-840)

The P0.1 manoeuvre was activated during 3 consecutive breaths and each P0.1vent was recorded. Then, three end-expiratory occlusions were activated to measure auto-PEEP offline.

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Tables E4 to E7 ASL 5000 settings

Table E4 ASL 5000 settings for inspiratory effort with **linear decay** and **obstructive** lung model

EFFORT MODEL	RR	Pmus (cmH_2O)	Increase (%)
1	20	3	10
2	20	3	15
3	20	3	30
4	20	3	35
5	20	6	10
6	20	6	15
7	20	6	30
8	20	6	35
9	20	10	10
10	20	10	15
11	20	10	30
12	20	10	35
13	20	15	10
14	20	15	15
15	20	15	30
16	20	15	35
17	20	20	10
18	20	20	15
19	20	20	30
20	20	20	35
21	20	25	10
22	20	25	15
23	20	25	30
24	20	25	35

Table E5 ASL 5000 settings for inspiratory effort with **linear decay** and **normal** lung model

EFFORT MODEL	RR	Pmus (cmH_2O)	Increase (%)	Low sensitive pressure trigger* (cmH_2O)
1	12	3	6	-2
2	12	3	9	-2
3	12	3	18	-2
4	12	3	21	-2
5	12	6	6	-4
6	12	6	9	-4
7	12	6	18	-4
8	12	6	21	-4
9	12	10	6	-5
10	12	10	9	-5
11	12	10	18	-5
12	12	10	21	-5
13	12	15	6	-5
14	12	15	9	-5
15	12	15	18	-5
16	12	15	21	-5
17	12	20	6	-5
18	12	20	9	-5
19	12	20	18	-5
20	12	20	21	-5
21	12	25	6	-5
22	12	25	9	-5
23	12	25	18	-5
24	12	25	21	-5

*applies only to the additional simulations when low sensitive pressure trigger was used in the Servo-u ventilator

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Table E6 ASL 5000 settings for inspiratory effort with **non-linear** decay and **obstructive** lung model

EFFORT MODEL	RR	Pmus (cmH_2O)	Increase (%)
1	20	3	10
2	20	3	15
3	20	3	30
4	20	6	10
5	20	6	15
6	20	6	30
7	20	10	10
8	20	10	15
9	20	10	30
10	20	15	10
11	20	15	15
12	20	15	30
13	20	20	10
14	20	20	15
15	20	20	30
16	20	25	10
17	20	25	15
18	20	25	30

Table E7 ASL 5000 settings for inspiratory effort with **non-linear** decay and **normal** lung model

EFFORT MODEL	RR	Pmus (cmH_2O)	Increase (%)
1	12	3	6
2	12	3	9
3	12	3	18
4	12	6	6
5	12	6	9
6	12	6	18
7	12	10	6
8	12	10	9
9	12	10	18
10	12	15	6
11	12	15	9
12	12	15	18
13	12	20	6
14	12	20	9
15	12	20	18
16	12	25	6
17	12	25	9
18	12	25	18

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Additional details regarding all signal analysis for the human data and the bench

Pressure-time product per breath (PTP/br) was averaged for one minute in *APRV/BIPAP* and *MYOTRAUMA studies.* In *APRV/BIPAP* the last minute of each ventilatory mode was analysed for stability. In *MYOTRAUMA* the first minute of the recording was analysed because no change in the ventilatory mode was performed prior to the recording and whole breath end-expiratory occlusions were performed during the recording. In *RegAIN*, the peak electrical activity of the diaphragm (EAdipeak) was averaged over 25 cycles at the end of each ventilatory condition. To avoid the influence of the occlusion on subsequent inspiratory efforts, two breaths after each occlusion were discarded. Breathing cycles with obvious artifact on the esophageal pressure tracing due to spasm were discarded.

Auto-PEEP was defined as the difference between the total end-expiratory pressure during an end-expiratory occlusion in the absence of effort and the set PEEP in the bench study. In the human data, auto-PEEP was defined as the difference between the esophageal pressure at the start of inspiratory effort and the esophageal pressure at zero flow.

Additional details regarding statistical analyses for the human data and the bench study

Sample size calculation

Patients

We estimated that a minimum of 25 tracings would be required to observe a correlation between P0.1ref and PTP/min with a coefficient of determination (R^2) higher than 0.3 with a 5% probability of a Type I error and 20% probability of a Type II error (http://www.sample-size.net/).

Bench

To estimate the 95% CI of the difference between P0.1vent and P0.1ref with a precision of 0.2 cmH_2O a minimum of 24 simulations were required for each ventilator (considering the reported SD of the difference between P0.1vent and P0.1ref for the first generation of Evita being 0.5 cmH_2O (22)).

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Figure legends

Figure E1. Relationship between effort per breath and per minute and reference P0.1 measured at the airway pressure (P0.1*ref*). Each dot corresponds to a patient in a clinical condition (tracing). Data from *APRV/PCV* study and *MYOTRAUMA* study are pooled together (N= 74 tracings in 26 patients). The fitted regression lines are drawn in blue, shaded grey area corresponds to 95% CI. 1A) and 1B) correspond to the relationship between P0.1*ref* and effort per minute ($PTP/_{min}$) -between-patient R^2 0.67, within-patient R^2 0.86- and P0.1*ref* and effort per breath ($PTP/_{br}$) -between-patient R^2 0.15, within-patient R^2 0.85- respectively. *Abbreviations*: $PTP/_{min}$= pressure-time product per minute; $PTP/_{br}$= pressure-time product per breath; P0.1*ref* = reference airway occlusion pressure measured at the airway pressure.

Figure E2. Bland and Altman plot showing accuracy and precision of P0.1*vent* compared to P0.1*ref* and influence of type of trigger during the Bench simulation in the Servo ventilators (Getinge). The difference between the average of three P0.1*vent* and average of three corresponding P0.1*ref* is plotted against the average of the two variables. Each dot is one simulation. Black horizontal continuous line represents mean bias and dashed lines upper and lower limits of agreement. Orange and green dots represent simulations without and with Auto-PEEP respectively. Regression line for the difference between P0.1*vent* and P0.1*ref* across the range of P0.1 values are plotted together with CI 95% for simulations with and without Auto-PEEP in orange and green respectively.
A) and **B)** represent the accuracy and precision of $P0.1_{vent}$ in the Servo-i ventilator when a linear and non-linear decay of inspiratory effort was simulated respectively. In both, a sensitive trigger was used (pressure = -1 cmH_2O or flow =2l/min randomly). **C)** and **D)** represent simulations using Servo-u ventilator. In both, same simulated inspiratory effort was run using a linear decay. **3C** represents simulations with and without Auto-PEEP and trigger was sensitive (pressure = -1 cmH_2O or flow =2l/min randomly). **3D** represents only simulations without Auto-PEEP and with a less sensitive pressure trigger (raging from -2 to -5 cmH_2O).

Abbreviations: P0.1 = airway occlusion pressure, $P0.1_{vent}$ = P0.1 displayed by the ventilator, $P0.1_{ref}$ = reference P0.1

Figure E3. Bland and Altman comparing accuracy and precision of P0.1*vent* compared to P0.1*ref* during the Bench simulation in GE Healthcare ventilators (Engström and R860). The difference between the average of three $P0.1_{vent}$ and average in three corresponding $P0.1_{ref}$ is plotted against the average of the two variables for each simulation. Black horizontal continuous line represents mean bias and dashed lines upper and lower limits of agreement. Orange and green dots represent simulations without and with Auto-PEEP respectively. Regression line for the difference between P0.1*vent* and P0.1*ref* across the range of P0.1 values are plotted together with CI 95% for simulations with and without Auto-PEEP in orange and green respectively.

A) Carescape R860 (GE Healthcare). A non-linear decay of inspiratory effort was simulated, **B)** Engström (GE Healthcare). A linear decay of inspiratory effort was simulated.

Abbreviations: P0.1 = airway occlusion pressure, $P0.1_{vent}$ = P0.1 displayed by the ventilator, $P0.1_{ref}$ = reference P0.1

Figure E4. Representative tracing of two simulated efforts in the bench connected to the Servo-u (Getinge) comparing the algorithm to measure P0.1 displayed by the ventilator (P0.1*vent*) and reference P0.1 measured at the airway pressure (P0.1*ref*). From top to

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bottom: airway pressure (Paw) and flow over time. Left panel (A), displays a weak inspiratory effort and right panel (B) a strong inspiratory effort. In each panel, an unoccluded breath is followed by a breath during and end-expiratory occlusion. The ventilator displays P0.1 estimated based on the trigger phase during the unoccluded breath: P0.1 measurement starts as soon as the pressure drops 0.5cmH_2O below PEEP (*), then drop in Paw is measured during the trigger phase (red continuous line) and extrapolated to 100 msec (red dotted line). P0.1ref is measured during an end-expiratory occlusion as the drop in Paw during the first 100 msec (red continuous line).
Of note, these tracings are only representative. They were acquired by measuring the signals between the Y-piece and simulator (ASL 5000), the ventilator measures P0.1*vent* close to the inspiratory valve. Details regarding the algorithm to measure P0.1vent by the Servo ventilator are unknown, present description is based on the document: Servo Education study guide (English version 1.13).

Abbreviations: Paw= airway pressure, P0.1*vent* = airway occlusion pressure displayed by the ventilator, $P0.1_{ref}$ = reference airway occlusion pressure measured at the airway pressure.

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Figure E1

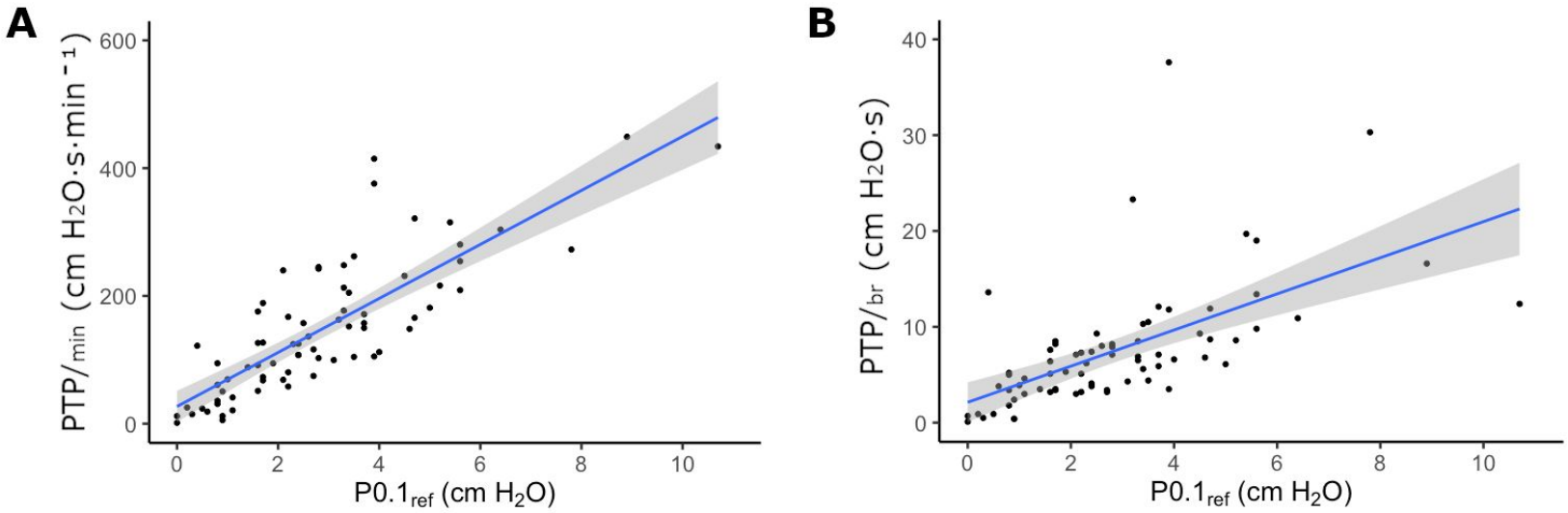

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Figure E2

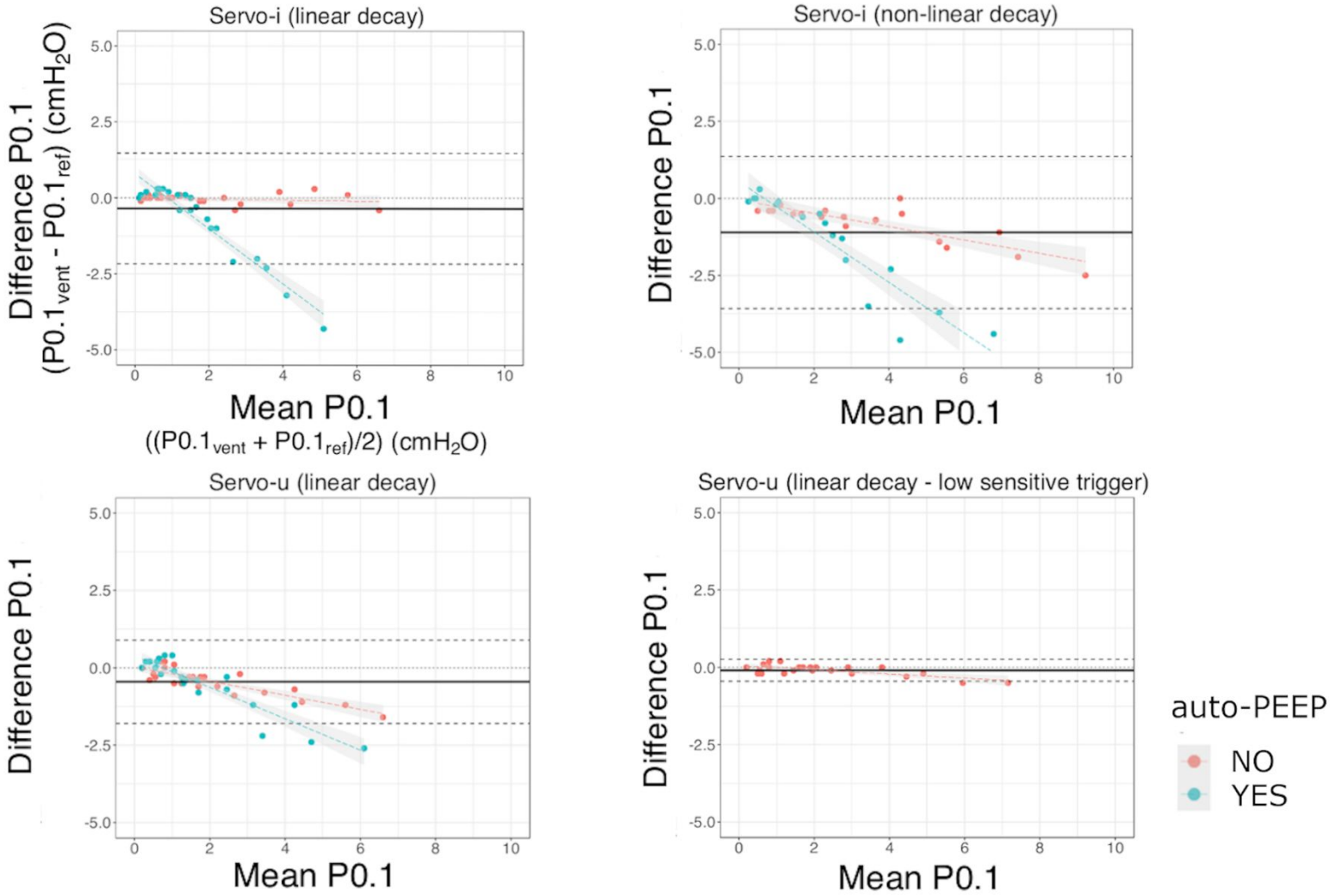

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Figure E3

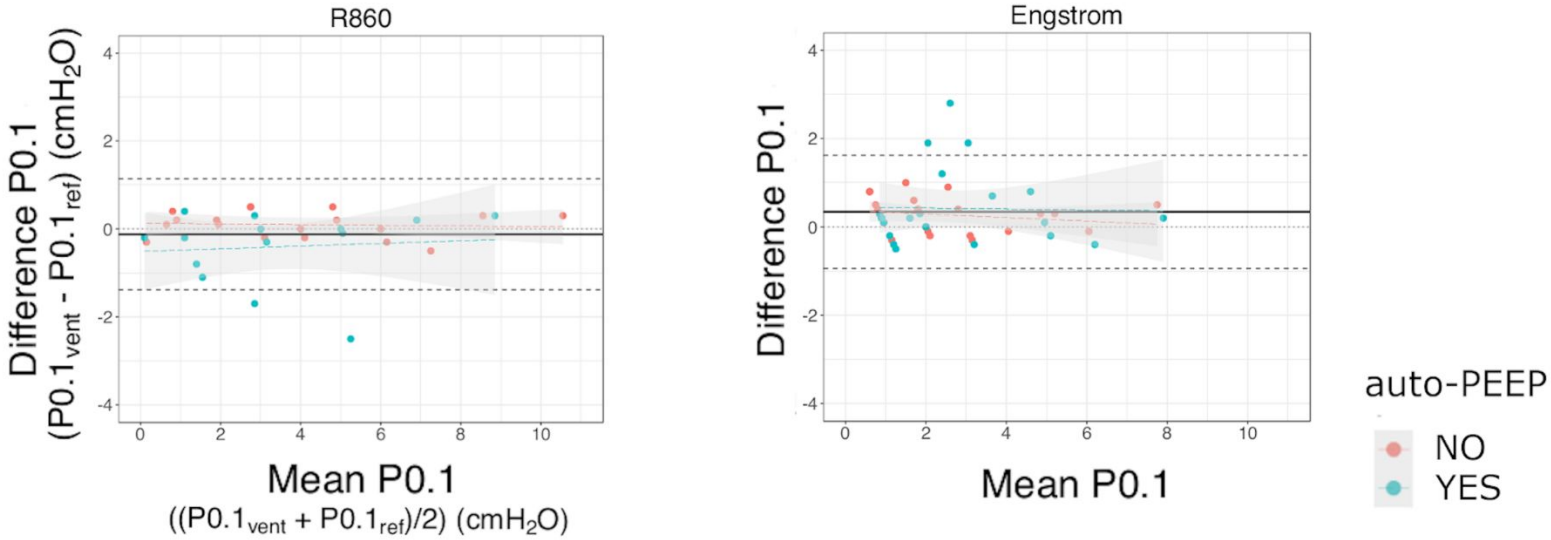

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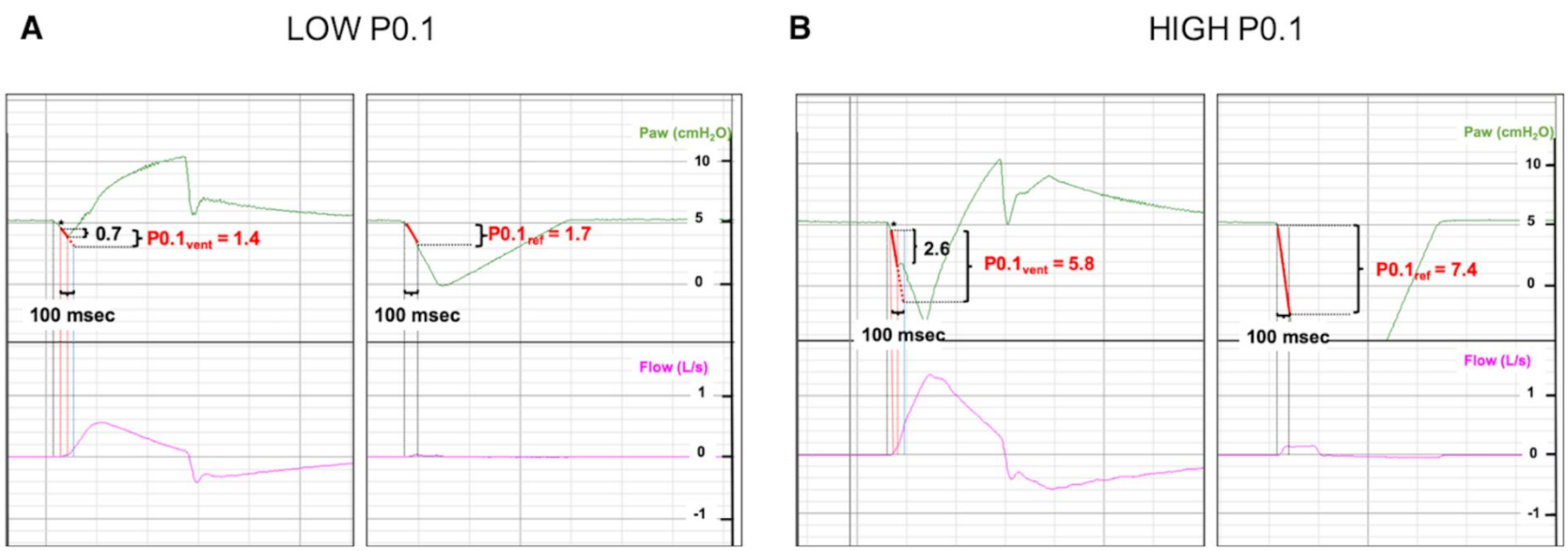
Figure E4



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