ANESTHESIOLOGY

Driving Pressure Is Associated with Outcome during Assisted Ventilation in Acute Respiratory Distress Syndrome

Giacomo Bellani, M.D., Ph.D., Alice Grassi, M.D., Simone Sosio, M.D., Stefano Gatti, M.D., Brian P. Kavanagh, M.B., Antonio Pesenti, M.D., Giuseppe Foti, M.D.

ANESTHESIOLOGY 2019; 131:594–604

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Higher driving pressure during controlled mechanical ventilation is known to be associated with increased mortality in patients with acute respiratory distress syndrome.
- Whereas patients with acute respiratory distress syndrome are initially managed with controlled mechanical ventilation, as they improve, they are transitioned to assisted ventilation. Whether higher driving pressure assessed during pressure support (assisted) ventilation can be reliably assessed and whether higher driving pressure is associated with worse outcomes in patients with acute respiratory distress syndrome has not been well studied.

What This Article Tells Us That Is New

- This study shows that in the majority of adult patients with acute respiratory distress syndrome, both driving pressure and respiratory system compliance can be reliably measured during pressure support (assisted) ventilation.
- Higher driving pressure measured during pressure support (assisted) ventilation significantly associates with increased intensive care unit mortality, whereas peak inspiratory pressure does not.
- Lower respiratory system compliance also significantly associates with increased intensive care unit mortality.

ABSTRACT

Background: Driving pressure, the difference between plateau pressure and positive end-expiratory pressure (PEEP), is closely associated with increased mortality in patients with acute respiratory distress syndrome (ARDS). Although this relationship has been demonstrated during controlled mechanical ventilation, plateau pressure is often not measured during spontaneous breathing because of concerns about validity. The objective of the present study is to verify whether driving pressure and respiratory system compliance are independently associated with increased mortality during assisted ventilation (*i.e.*, pressure support ventilation).

Methods: This is a retrospective cohort study conducted on 154 patients with ARDS in whom plateau pressure during the first three days of assisted ventilation was available. Associations between driving pressure, respiratory system compliance, and survival were assessed by univariable and multivariable analysis. In patients who underwent a computed tomography scan (n = 23) during the stage of assisted ventilation, the quantity of aerated lung was compared with respiratory system compliance measured on the same date.

Results: In contrast to controlled mechanical ventilation, plateau pressure during assisted ventilation was higher than the sum of PEEP and pressure support (peak pressure). Driving pressure was higher (11 [9–14] *vs.* 10 [8–11] cm H_2O; $P = 0.004$); compliance was lower (40 [30–50] *vs.* 51 [42–61] ml · cm H_2O^{-1}; $P < 0.001$); and peak pressure was similar, in nonsurvivors *versus* survivors. Lower respiratory system compliance (odds ratio, 0.92 [0.88–0.96]) and higher driving pressure (odds ratio, 1.34 [1.12–1.61]) were each independently associated with increased risk of death. Respiratory system compliance was correlated with the aerated lung volume (n = 23, r = 0.69, $P < 0.0001$).

Conclusions: In patients with ARDS, plateau pressure, driving pressure, and respiratory system compliance can be measured during assisted ventilation, and both higher driving pressure and lower compliance are associated with increased mortality.

(ANESTHESIOLOGY 2019; 131:594–604)

Driving pressure, the difference between plateau pressure and positive end-expiratory pressure (PEEP), is closely associated with outcome in patients with acute respiratory distress syndrome (ARDS), and higher levels of driving pressure predict mortality independently of PEEP or tidal volume (V_T).[1,2] Whereas higher V_T increases mortality in ARDS,[3] there is substantial variability among patients in terms of static respiratory system, which relates to the amount of lung volume available for aeration.[4] Driving pressure incorporates V_T

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). For a downloadable PPT slide containing this article's citation information, please visit https://anesthesiology.pubs.asahq.org/ss/downloadable_slide.aspx. The data presented in this manuscript were presented at LIVES 2018 (European Society of Intensive Care Medicine annual congress), held in Paris on October 22, 2018, and at Critical Care Canada Forum, held in Toronto on November 7, 2018.

Submitted for publication November 22, 2018. Accepted for publication April 15, 2019. From the Department of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy (G.B., A.G., S.S., S.G., G.F.); Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy (G.B., A.G., S.S., S.G., G.F.); Departments of Critical Care Medicine and Anesthesia, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada (B.P.K.); Department of Anesthesia, Critical Care and Emergency Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy (A.P.).

 Anesthesiology 2019; 131:594–604. DOI: 10.1097/ALN.0000000000002846

and respiratory system compliance (driving pressure = V_T/respiratory system compliance) and simultaneously accounts for the delivered V_T (higher is adverse) and the underlying respiratory system compliance (lower is adverse). The association between driving pressure and outcome has been well characterized during controlled mechanical ventilation,[1,2,5,6] and provided plateau pressure is accurately recorded—a simple task with modern ventilators—the use of this measurement during controlled ventilation is straightforward. Perhaps the most important limitation is the lack of outcome data after randomization to targeted levels of driving pressure.[7]

In the presence of spontaneous breathing effort, clinicians do not usually measure plateau pressure, and therefore do not record driving pressure, for several reasons. An inspiratory hold to measure plateau pressure may be unreliable if the breathing effort distorts the imposed hold[1,8,9]; however, it is easy to confirm zero flow and accurately measure plateau pressure (and therefore driving pressure) during spontaneous effort, and this has previously been confirmed.[10,11] In addition, although the concept of plateau pressure during controlled ventilation is straightforward (invariably, plateau pressure is lower than peak pressure; fig. 1), the nature of plateau pressure during assisted ventilation is not intuitive. An inspiratory hold during an assisted breath contains a V_T that is developed from two contributions: the ventilator and the patient's effort. Depending upon the magnitude of the patient effort (negative pressure) relative to that of the ventilator (positive pressure), the plateau pressure may be higher than the peak pressure.[12–14] In keeping with common practice, however, we still refer to the sum of PEEP and pressure support as peak pressure because this is the highest pressure recorded on the ventilator screen during tidal breathing. This occurs because the positive and negative pressures are additive, and the V_T produced is greater than could have been generated by the ventilator pressure alone. Thus, at zero flow, the large V_T—applied to the same respiratory system compliance—yields a plateau pressure greater than peak pressure.[15]

Because assisted ventilation is necessary and desirable at some stage in every patient with ARDS, prognostication

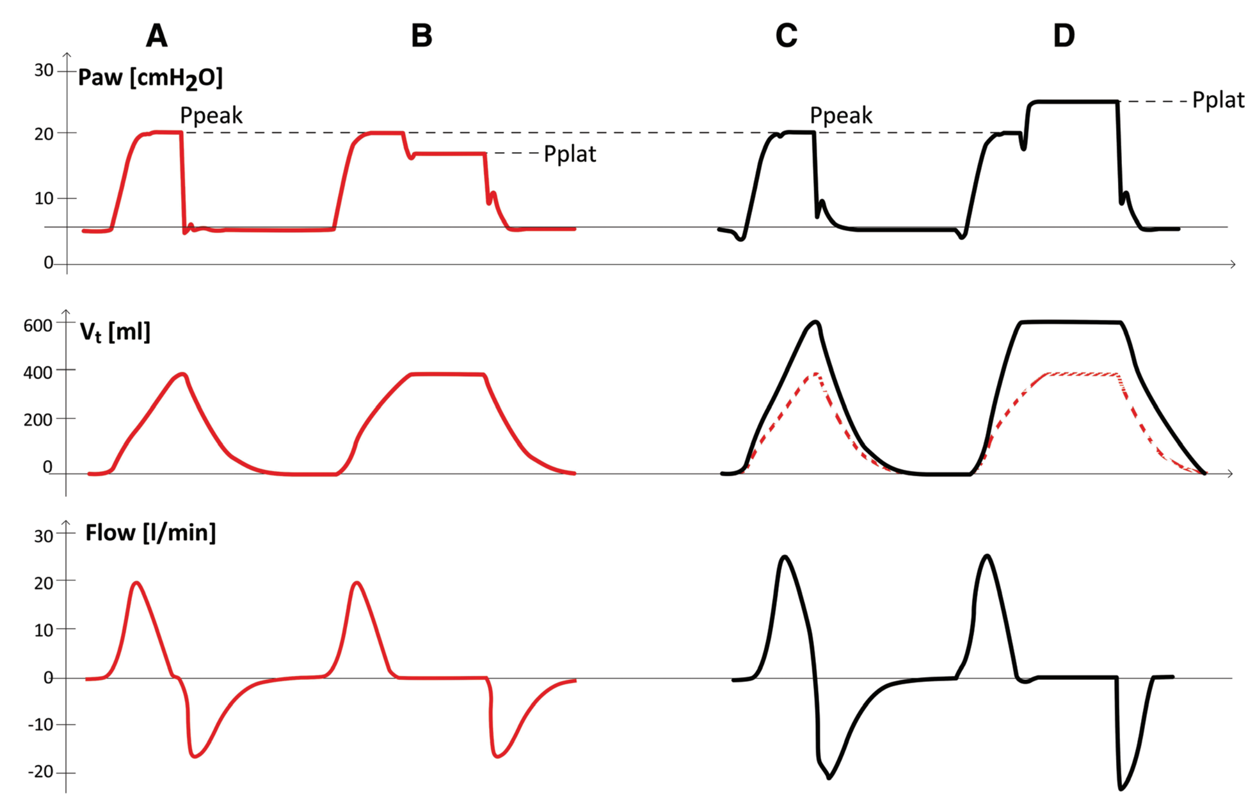

Fig. 1. Schematic examples of uninterrupted breaths and end-inspiratory holds. In pressure controlled ventilation (*A* and *B*), an end-inspiratory occlusion (*B*) reveals a plateau pressure that is lower than peak inspiratory pressure; this is due to the abolition of gas inflow and its redistribution within the lung. During pressure support ventilation (*C* and *D*), the spontaneous efforts leads—at the same peak inspiratory pressure—to a greater tidal volume than during pressure controlled ventilation (*red dashed line*). This is because gas inflow is caused not only by the airway pressure (generated by the ventilator, and displayed), but also by the patient's effort. Hence, when inspiration is occluded (*D*), plateau pressure is greater than during equivalent pressure-controlled ventilation, and is greater than peak inspiratory pressure because the inspiratory muscles have relaxed and no longer tend to reduce the airway pressure. Paw, airway pressure; $P_{peak,}$ peak airway pressure; P_{plat}, plateau airway pressure; V_T, tidal volume.

and management targets during assisted ventilation will be required. In our intensive care unit—as in other institutions[16]—we initially manage patients with ARDS using controlled ventilation and, as the condition improves, convert to assisted ventilation (pressure support ventilation); we traditionally record plateau pressure for each patient each day.

Here, to confirm that driving pressure could be a valid target during assisted ventilation we test the hypothesis that driving pressure is independently associated with outcome during assisted ventilation. In addition, to confirm the biologic plausibility of this link, we examined the relationship between respiratory system compliance and the volume of aerated lung (measured on computed tomography scans) during assisted ventilation, as has previously been reported during controlled ventilation.[17,18]

Materials and Methods

This is a single center, cohort retrospective study. The institutional ethics committee (Azienda Socio Sanitaria Territoriale Monza, Italy) approved the study and waived the need for informed consent, because of the observational nature of the study. The study was entirely conducted on data collected for clinical purposes and regarding patients admitted to the General Intensive Care Unit (ICU) of San Gerardo Hospital, Monza, Italy.

Patient Selection

We screened all patients who underwent at least four consecutive days of invasive mechanical ventilation in the period from June 2014 to December 2017. We enrolled patients with the following inclusion criteria:

- Age greater than 18 yr
- At least three consecutive days of assisted ventilation in pressure support mode after at least 24 consecutive hours of controlled mechanical ventilation
- Diagnosis of ARDS according to the Berlin Definition[19] at any time point during the ICU stay

The presence of diagnostic criteria for ARDS was assessed by the data reported in the medical records. Chest radiographs were reviewed to assess the presence of bilateral infiltrates by two intensivists (A.G., S.S.), and discordant opinions were resolved by a third intensivist (G.B.). Patients who died before being switched to assisted ventilation, by definition, could not fulfill the inclusion criteria and were not included in the study.

Exclusion criteria were:

- Pregnancy
- Air leaks (*bronchopleural fistula, pneumothorax*)

Data Extraction

The Electronic Medical record (Innovian, Draeger, Germany) of each patient was reviewed to extract the following data: demographic data (age, sex, body weight, Body Mass Index), main preexisting comorbidities, primary diagnosis responsible for the need for mechanical ventilation, Sequential Organ Failure Assessment, and Simplified Acute Physiology Score II scores at ICU admission. Mechanical ventilation parameters during the first and last day of controlled mechanical ventilation and during the first three days of assisted ventilation when available (*i.e.*, charted in the medical record) were registered. To account for missing plateau pressure values, we averaged the plateau pressure over the first three days of assisted ventilation, and these values were used for the primary analysis. The collected parameters were: V_T, respiratory rate, fraction of inspired oxygen, PEEP, level of pressure support, peak pressure, and plateau pressure (fig. 1). Driving pressure and respiratory system compliance were calculated at each time point according to standard formulas.[20] Because respiratory system compliance depends not only on the severity of the disease[4] but also on the size of the patient's lung during health, respiratory system compliance was normalized to predicted respiratory system[21] to make this measurement comparable in a cohort of patients with different heights. Pressure muscle index was calculated (pressure muscle index = peak pressure − plateau pressure), as previously described,[15] which represents the pressure increase in the respiratory system attributable to patient relaxation, and is correlated with the work of breathing.[15] Blood gas data and clinical status were recorded.

Standard Methodology to Assess Plateau Pressure during Pressure Support Ventilation

As a standard practice in our ICU, an inspiratory hold is performed at least once per day by the treating physician in every patient with ARDS, during either controlled or assisted mechanical ventilation. The criteria normally used by the clinicians to assess the reliability of the plateau pressure measurement during spontaneous breathing efforts are:

- The duration of the occlusion is greater than 2 s
- Airflow equals zero ml/sec
- Plateau pressure is flat
- No visible thoracic or abdominal movement, as assessed by directly looking at the patient during the occlusion

An example of a reliable plateau pressure during assisted ventilation was illustrated.[12] On the contrary, the presence of unstable plateau pressure (*i.e.*, slow ramp to reach a plateau pressure, curve plateau pressure) indicates ongoing inspiratory or expiratory effort, or a leak and leads to discarding the measurement.

Computed Tomography

Images were downloaded for those patients who underwent computed tomography of the chest for clinical purposes while receiving assisted ventilation. Scans were acquired during uninterrupted tidal ventilation. The ventilation parameters listed above were obtained from the time of the computed tomography scan. Lung scans (spiral computed tomography, apex to diaphragm; Philips Brilliance 16 slice) were taken and images analyzed offline (ImageJ, National Institutes of Health, USA) to determine the quantity of lung pixels for each slice, and the mean density of the entire lungs (in Hounsfield Units). Standard calculations for total lung volume (voxel size × total number of voxels) and gas volume (total volume × [mean density/−1024]) were used.[22] For each lung, the volume of normo-, hypo-, and hyperaerated areas was calculated as a percentage of total lung volume and by using the ranges of Hounsfield Units indicated in Gattinoni *et al.*[22] Then the following formula was applied: aerated lung volume (ml) = normoaerated lung volume + hyperaerated lung volume.

Study Endpoints

The primary endpoint was the association between ventilation parameters (peak pressure, driving pressure, and respiratory system compliance) collected during the first three days of assisted ventilation and ICU mortality. The secondary endpoint was the association between respiratory system compliance and the volume of aerated lung as measured by computed tomography, during assisted ventilation.

Statistical Analysis

This study shows the *a priori* primary analysis of the collected data. Outliers data were verified in the source documents and, once confirmed, were left unchanged in the database. No formal statistical power calculation was conducted before the study. We enrolled all patients (who satisfied inclusion criteria) over the 3.5-yr period before the beginning of the analysis. Clinical variables and respiratory parameters were compared between ICU survivors and nonsurvivors. Analysis were performed using SPSS software (IBM, USA). The normal distribution of all continuous variables was verified by the Shapiro–Wilk test. Data are expressed as mean ± SD, or as median [interquartile range], for normally or nonnormally distributed variables, respectively. Univariate analysis was performed by two-tailed *t* test for independent samples for normally distributed continuous data, and two-tailed Mann–Whitney for nonnormally distributed continuous data, and χ^2 test for categorical data. $P < 0.05$ was considered statistically significant. A sensitivity analysis was performed on the values collected on the first day of assisted ventilation and on the maximum and minimum values of driving pressure. The most clinically meaningful variables were introduced into a multivariable logistic regression model. Absence of collinearity between variables included in the multivariate analysis was assessed by variance inflation factor, nevertheless we ran two separated models for respiratory system compliance and driving pressure, because on a physiologic perspective they are closely related. Patients were divided into quartiles of driving pressure, respiratory system compliance, and peak pressure, the ICU mortality rate for each quartile was computed, and the mortality among quartiles compared using a χ^2 test with linear by linear association. Although the primary analysis took into account the values averaged over the first 3 days of assisted ventilation, we performed additional sensitivity analyses (1) on the data collected during the first day of assisted ventilation, and (2) on the highest and (3) lowest driving pressure collected. The association between respiratory system compliance (absolute and normalized) and aerated lung volume during assisted ventilation was determined by linear Spearman correlation.

Results

From a total of 1,981 patients screened, 167 ARDS patients converted from controlled to assisted mechanical ventilation, but plateau pressure values were available for 154; thus, 154 were included in the final analysis (fig. 2).

Controlled Ventilation

The demographic (table 1) and respiratory (table 2) data at baseline during controlled ventilation are presented. Low V_T was used, and 34 of 154 patients (22%) died in ICU. Age, duration of controlled ventilation, and organ dysfunction score were greater in nonsurvivors *versus* survivors; as expected, plateau pressure was less than peak pressure (tables 1 and 2). On the final day of controlled ventilation, driving pressure was higher (13 ± 3 *vs.* 10 ± 2 cm H_2O, $P < 0.001$) and compliance lower (35 ± 13 *vs.* 47 ± 16 ml/cm H_2O, $P < 0.001$) in nonsurvivors *versus* survivors.

Assisted Ventilation

Eighteen percent of plateau pressure values were missing from the first 3 days of assisted ventilation. To corroborate

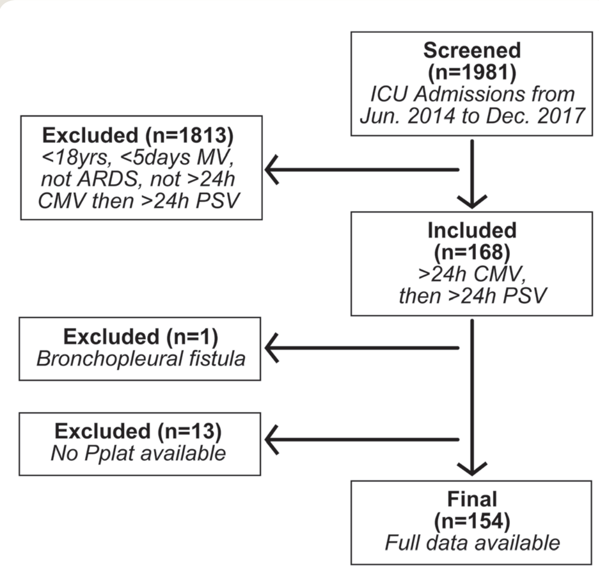

Fig. 2. Study flowchart. ARDS, acute respiratory distress syndrome; CMV, controlled mechanical ventilation; MV, mechanical ventilation; P_{plat}, plateau pressure; PSV, pressure support ventilation.

Table 1. General Population Data

	Overall (n = 154)	Nonsurvivors (n = 34)	Survivors (n = 120)	*P* Value
Age, yr	63 [49–72]	71 [64–76]	59 [46–70]	< 0.001
Male, n (%)	107 (69)	24 (71)	83 (69)	0.874
Body mass index, kg · m^{-2}	26 [23–29]	25 [22–28]	26 [24–30]	0.149
Mechanical ventilation, days	15 [9–22]	17 [10–24]	14 [9–22]	0.390
Controlled mechanical ventilation, days	4 [2–8]	7 [3–13]	3 [2–7]	0.007
SAPS on admission	44 ± 14	49 ± 15	43 ± 14	0.039
SOFA on admission	9 [6–11]	10 [7–13]	8 [6–11]	0.032
Vasopressors, days	6 [3–11]	11 [4–20]	6 [3–10]	0.005
Renal dialysis, days	0 [0–0]	0 [0–4]	0 [0–0]	0.013
ICU length of stay, days	16 [10–25]	18 [10–25]	16 [11–25]	0.798
Pulmonary ARDS, n (%)	101 (66)	19 (56)	82 (68)	0.177
Nonpulmonary ARDS (n, %)	53 (34)	15 (44)	38 (33)	

Data are presented as median [interquartile range] or mean ± SD or as absolute number (percentage). ARDS, acute respiratory distress syndrome; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

Table 2. Respiratory Data on the First Day of Controlled Mechanical Ventilation

	Overall (n = 154)	Nonsurvivors (n = 34)	Survivors (n = 120)	*P* Value
Peak pressure, cm H_2O	29 [24–33]	29 [24–35]	29 [24–32]	0.827
Plateau pressure, cm H_2O	24 ± 5	25 ± 4	24 ± 5	0.206
PEEP, cm H_2O	12 [10–15]	11 [8–14]	12 [10–15]	0.317
Driving pressure, cm H_2O	11 [9–13]	12 [10–17]	10 [9–13]	0.049
Tidal volume, ml	430 [376–480]	450 [375–500]	425 [373–480]	0.446
Tidal volume, ml · kg^{-1}	6.6 ± 1.5	6.7 ± 1.8	6.6 ± 1.4	0.609
Respiratory rate, min^{-1}	18 [12–24]	18 [12–25]	19 [12–24]	0.866
Compliance of respiratory system, ml/cm H_2O	39 [29–48]	35 [24–48]	40 [30–49]	0.210
Compliance of respiratory system, % predicted	34 [24–43]	28 [17–42]	34 [25–44]	0.085
Pao_2, mmHg	95 [82–113]	91 [82–108]	97 [82–114]	0.311
Pao_2/Fio_2 ratio	142 [109–206]	133 [113–172]	152 [108–213]	0.358
$PaCO_2$, mmHg	43 [38–50]	42 [36–50]	43 [38–50]	0.898
pH	7.39 [7.35–7.43]	7.36 [7.31–7.39]	7.40 [7.35–7.43]	0.002

Data are presented as median [interquartile range] or mean ± SD. FiO_2, fraction of inspired oxygen tension; PEEP, positive end-expiratory pressure.

the strength of respiratory system compliance measurement during assisted mechanical ventilation, we built a correlation between respiratory system compliance measured during the last day of controlled mechanical ventilation and the average respiratory system compliance measured during the first 3 days of assisted ventilation. The correlation was moderately strong ($R = 0.79$, Supplemental Digital Content 1, http://links.lww.com/ALN/B988); a Bland and Altman between these two measurements showed that respiratory system compliance measured during assisted ventilation tended to be higher than respiratory system compliance measured during controlled ventilation (Supplemental Digital Content 2, http://links.lww.com/ALN/B989). The ventilator parameters during assisted ventilation are shown, and the characteristics of nonsurvivors included higher driving pressure and lower respiratory system compliance (absolute, normalized; table 3). Peak pressure was not different in survivors *versus* nonsurvivors, and during assisted ventilation, plateau pressure was higher than peak pressure (table 3). The same result was obtained when the analysis was repeated using only values collected on the first day of assisted ventilation (table 4). Similarly, the value of driving pressure was higher in nonsurvivors *versus* survivors when analysis was restricted to the maximal (12 [10–15] *vs.* 11 [9–12] $P = 0.007$) or minimal (10 [8–13] *vs.* 9 [7–10] $P = 0.004$) value of the first 3 days of assisted ventilation.

To determine the strength of the relationship between driving pressure and outcome during assisted ventilation, two approaches were taken. First, multivariable analysis was undertaken of the most clinically meaningful variables at the beginning of the phase of pressure support ventilation (driving pressure or predicted respiratory system compliance, PEEP, Pao_2/fractional inspired oxygen tension [Fio_2], pH) and age and Sequential Organ Failure Assessment to take into account baseline severity. Higher driving pressure and respiratory system compliance, among other factors, were independently associated with nonsurvival

Table 3. Data Averaged over the First Three Days of Assisted Ventilation

	Overall (n = 154)	Nonsurvivors (n = 34)	Survivors (n = 120)	*P* Value
Assisted mechanical ventilation, days	9 [5–16]	7 [5–14]	10 [6–17]	0.133
Pressure support, cm H_2O	10 ± 3	10 ± 3	9 ± 3	0.073
Peak pressure, cm H_2O	21 ± 4	20 ± 4	21 ± 5	0.359
Plateau pressure, cm H_2O	22 [19–25]	22 [19–25]	22 [19–25]	0.893
PEEP, cm H_2O	11 ± 3	10 ± 3	12 ± 3	0.010
Driving pressure, cm H_2O	10 [9–12]	11 [9–14]	10 [8–11]	0.004
Tidal volume, ml	480 ± 106	433 ± 100	493 ± 104	0.003
Tidal volume, ml · kg^{-1}	7.4 ± 1.6	6.7 ± 1.5	7.6 ± 1.6	0.002
Respiratory rate, min^{-1}	16 [13–18]	17 [14–20]	15 [13–18]	0.004
Pressure muscle index, cm H_2O	1 [0–2]	2 [0–3]	0 [0–2]	0.053
Compliance of respiratory system, mL/cm H_2O	49 [39–60]	40 [30–50]	51 [42–61]	< 0.001
Compliance of respiratory system, % predicted	41 [32–50]	35 [24–42]	44 [33–53]	0.001
Pao_2, mmHg	100 [90–109]	102 [88–107]	100 [90–109]	0.317
Pao_2/Fio_2 ratio	228 [193–286]	224 [174–259]	233 [201–291]	0.121
$PaCO_2$, mmHg	45 [42–50]	45 [42–51]	45 [42–50]	0.855
pH	7.42 [7.40–7.45]	7.42 [7.39–7.44]	7.42 [7.40–7.45]	0.373

Data are presented as median [interquartile range] or mean ± SD. FiO_2, fraction of inspired oxygen tension; PEEP, positive end-expiratory pressure.

Table 4. Data on the First Day of Assisted Ventilation

	Overall (n = 136)	Nonsurvivors (n = 27)	Survivors (n = 109)	*P* Value
Pressure support, cm H_2O	10 ± 3	11 ± 4	10 ± 3	0.040
Peak pressure, cm H_2O	22 ± 5	21 ± 4	22 ± 5	0.482
Plateau pressure, cm H_2O	22 [19 to 25]	23 [18 to 26]	22 [20 to 25]	0.844
PEEP, cm H_2O	12 ± 3	10 ± 3	12 ± 4	0.002
Driving pressure, cm H_2O	10 [8 to 12]	12 [9 to 14]	10 [8 to 12]	0.016
Tidal volume, ml	479 ± 114	446 ± 114	488 ± 113	0.056
Tidal volume, ml · kg^{-1}	7.4 ± 1.8	6.9 ± 1.7	7.6 ± 1.7	0.037
Respiratory rate, min^{-1}	15 [12 to 19]	17 [14 to 20]	15 [12 to 19]	0.037
Pressure muscle index, cm H_2O	0 [-1 to 2]	1 [0 to 3]	0 [-1 to 1]	0.049
Compliance of respiratory system, mL/cm H_2O	47 [38 to 59]	42 [29 to 50]	48 [40 to 60]	0.017
Compliance of respiratory system, % predicted	38 [31 to 52]	35 [25 to 40]	40 [32 to 52]	0.026
Pao_2, mmHg	98 [86 to 113]	96 [82 to 111]	99 [87 to 114]	0.203
Pao_2/Fio_2 ratio	225 [178 to 278]	205 [165 to 256]	229 [185 to 284]	0.043
$PaCO_2$, mmHg	45 [42 to 50]	46 [42 to 50]	45 [42 to 50]	0.998
pH	7.42 [7.38 to 7.45]	7.42 [7.39 to 7.44]	7.42 [7.38 to 7.45]	0.605

Data are presented as median [interquartile range] or mean ± SD. FiO_2, fraction of inspired oxygen tension; PEEP, positive end-expiratory pressure.

(table 5). Because driving pressure and respiratory system compliance are highly correlated (by definition, driving pressure = V_T/respiratory system compliance) the analysis was run separately with driving pressure included (and respiratory system compliance excluded), and then with respiratory system compliance included (and driving pressure excluded; table 5). Second, the mortality data were inspected after categorization of patients into quartiles of driving pressure, peak pressure, and respiratory system compliance (fig. 3). Mortality increased across increasing quartiles of driving pressure and decreased across decreasing quartiles of respiratory system compliance, but there was no relationship between mortality and peak pressure (fig. 3). To account for baseline severity, we compared age and Sequential Organ Failure Assessment along quartiles of driving pressure showing that these were not different along quartiles (Supplemental Digital Content 3, http://links.lww.com/ALN/B990).

Finally, the aerated lung volume was examined in computed tomography scans of 23 patients for whom a scan during the assisted ventilation period was available. There was a moderate correlation between the aerated lung volume *versus* absolute respiratory system compliance (R = 0.69, $P < 0.0001$), and between the ratio of aerated to total lung volume *versus* the ratio of actual to predicted respiratory system compliance (fig. 4).

Table 5. Variables Independently Associated with Risk of ICU Death

	Odds Ratio (95% CI)	*P* Value
Model 1 (includes driving pressure)		
Age, yr	1.05 (1.02–1.09)	0.004
SOFA score	1.20 (1.05–1.38)	0.007
PEEP during pressure support ventilation, cm H_2O	0.84 (0.72–0.98)	0.028
ΔP during pressure support ventilation, cm H_2O	1.34 (1.12–1.61)	0.001
Pa_{O_2}/F_{IO_2} during pressure support ventilation	1.00 (0.99–1.01)	0.666
pH during pressure support ventilation	1.12 (0.25–4.98)	0.884
MODEL 2 (includes respiratory system compliance)		
Age, yr	1.07 (1.03–1.10)	0.001
SOFA score	1.20 (1.05–1.37)	0.008
PEEP during pressure support ventilation, cm H_2O	0.83 (0.71–0.97)	0.018
Compliance of respiratory system, % of predicted	0.92 (0.88–0.96)	< 0.001
Pa_{O_2}/F_{IO_2} during pressure support ventilation	1.00 (1.00–1.01)	0.788
pH during pressure support ventilation	0.70 (0.16–3.11)	0.634

ΔP, driving pressure; FiO_2, fraction of inspired oxygen tension; ICU, intensive care unit; PEEP, positive end-expiratory pressure; SOFA, Sequential Organ Failure Assessment.

Discussion

The main insight from these data is that routinely recorded driving pressure during pressure support ventilation is closely associated with outcome, as has been reported for driving pressure recorded during controlled ventilation.[1,2] Moreover, the findings are corroborated by close correlation between driving pressure (bedside mechanics) and volume of aerated lung (computed tomography scan) during assisted ventilation—also reported during controlled ventilation[17,22]—and this finding confers pathophysiological plausibility. In addition, plateau pressure is seldom measured and sometimes believed inaccurate[1,8,9] during assisted ventilation, but the current data support its plausibility as a potentially important clinical parameter.

Several lines of evidence point to the validity of driving pressure measurement during assisted ventilation. Although the bedside calculation of driving pressure is simple (driving pressure = plateau pressure − PEEP), the interpretation of plateau pressure is not intuitive. During controlled ventilation, plateau pressure is always lower than peak pressure, and this is attributable to the resistive (classic or ohmic and viscoelastic) pressure component. In contrast, during assisted ventilation plateau pressure may be higher than peak pressure, because this transition involves two opposite pressure changes: a pressure drop due to disappearance of inspiratory flow, as well as a pressure increase due to relaxation (of previously contracting) inspiratory muscles.[23] Because the flow profile in pressure support ventilation is typically decelerating, the first term is usually minimal. Indeed the difference between plateau pressure and peak pressure during pressure support ventilation, termed the pressure muscle index, is an accurate indicator of patient's work of breathing.[11] Once relaxation occurs the lungs are no longer being ventilated, and the plateau pressure is independent of whether the background mode of ventilation is controlled or assisted. Thus, for a given V_T and respiratory system compliance, the plateau pressure will be the same whether the contribution from the ventilator was large and from the patient was small, or *vice versa*, regardless of the mode of ventilation. Moreover, because plateau pressure is measured in the absence of flow, its value will not be affected by the classic (ohmic) resistive pressure drop[24]; however, the viscoelastic resistance might lead to a progressive decline of plateau pressure, depending on the duration of the occlusion, which, because of the retrospective nature of the study, was not standardized but usually lasted approximately 2s.

One concern during assisted ventilation is that plateau pressure might be overestimated if expiratory muscle contraction occurs during the inspiratory hold. This occurrence leads to a steadily increasing airway pressure during the airway occlusion; such traces are considered unreliable and are discarded. Eighteen percent of plateau pressure data were missing during the first 3 days of assisted ventilation, although we cannot determine in this retrospective whether these data were not measured, measured and considered unreliable, or for some other reason not recorded. However, we believe that about 10% of all plateau pressure measurements made during assisted breathing were unreliable, based on previously published data from our center, where 90% of measurements were assessed and considered

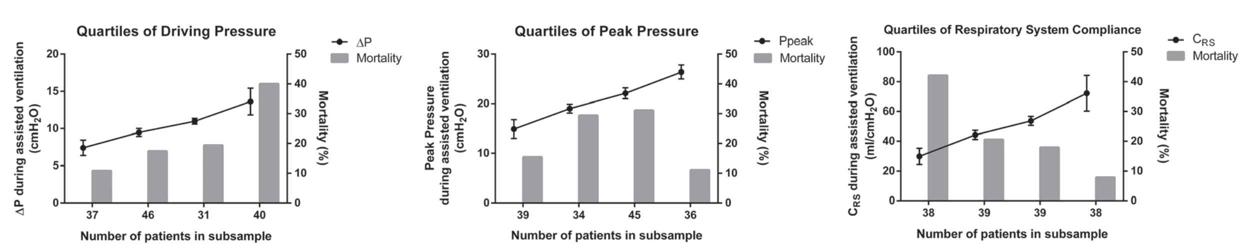

Fig. 3. Plots represent mortality rates of patients grouped according to quartiles of driving pressure (ΔP), peak airway pressure (P_{peak}; *i.e.*, P_{peak} = PEEP + pressure support level), and respiratory system compliance (C_{RS}). Mortality increased across quartiles of increasing ΔP (P = 0.002), decreased with increasing C_{RS} (P < 0.001), but was unrelated to P_{peak} (P = 0.831).

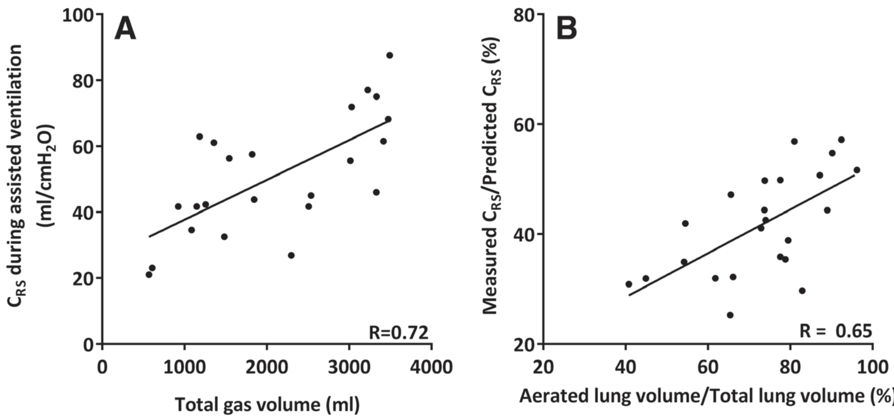

Fig. 4. Respiratory system compliance (C_{RS}) is well correlated to the total gas volume measured by computed tomography (*A*) during assisted ventilation, as previously demonstrated during controlled ventilation. Moreover, the C_{RS} normalized by the expected value of compliance, which takes into account the patient's body size, is correlated with aerated lung expressed as a fraction of total lung volume (*B*).

reliable.[10] Sensitivity analysis performed on different sampling conditions (first day only, highest and lowest driving pressure) confirmed the findings of the main analysis.

We provide additional corroboration of the reliability of driving pressure by demonstrating a close correlation between the respiratory system compliance (whose measurement incorporates driving pressure) and the volume of aerated lung as determined by computed tomography scan (fig. 4A), where both assessments were performed during assisted ventilation. Moreover, we also show that the respiratory system compliance expressed as a fraction of predicted respiratory system compliance was similarly correlated with the volume of aerated lung expressed as a fraction of the total lung volume (fig. 4B). These relationships have previously been demonstrated during controlled ventilation, and provide pathophysiological support that the values obtained for respiratory system compliance, a key component of driving pressure, are appropriate.

Finally, the relationship between driving pressure and outcome provides additional evidence that driving pressure—because it is prognostic, albeit not necessarily causal—is likely to be valid. Plateau pressure is strongly associated with outcome, and the association between driving pressure and outcome during controlled ventilation is increasingly established[7]; but, this has not been previously reported during assisted ventilation. Prognostic markers, as well as appropriate ventilator targets, are a major unmet need during assisted ventilation, for several reasons. First, although temporary paralysis may improve outcome,[25] the consequences of inadequate diaphragmatic effort are becoming better understood. In particular, disuse atrophy can lead to difficult weaning and prolonged duration of ventilation and length of ICU stay.[26] Second, all survivors who ultimately wean from mechanical ventilation need to breathe spontaneously; although this can be accomplished using intermitted unassisted breathing in the course of controlled ventilation (*e.g.*, unassisted T-piece weans), the majority of patients progress from controlled to assisted ventilation. Third, although traditional targets such as V_T and plateau pressure[27] are well characterized during controlled ventilation, data supporting these as either prognostic markers or management targets during assisted ventilation are lacking. Indeed, simple limitation of V_T in the presence of strong spontaneous effort can result in lung injury from double triggering (attributable to short inspiratory time)[28] or negative-pressure edema.[29] Therefore, because driving pressure incorporates both delivered V_T and respiratory system compliance (as during controlled ventilation), it is a rational candidate as a prognostic marker and, if validated, as a management target during assisted ventilation.

This study has important limitations. The design is retrospective (and obviously, not randomized); however, the use of data that were recorded for routine clinical care supports the feasibility of the approach. Because this is a single-center study, prospective, multi-center validation will be needed.

Calculation of plateau pressure during assisted ventilation shares all the limitations of its measurement during controlled ventilation. In particular there is insensitivity to intratidal recruitment–derecruitment and an inability to differentiate between the compliance of the chest wall and that of the lung.

The calculation of driving pressure and respiratory system compliance should take into account the total PEEP, which includes intrinsic PEEP, and this measure was not available in our patients. In the presence of spontaneous breathing, this value slightly varies on a breath-to-breath basis and requires esophageal manometry for accurate estimation. Thus, some driving pressure measurements may be overestimated.

The data used for this study almost certainly influenced patient management; in fact, clinicians might have reacted to a high driving pressure with different means of reducing it (*e.g.*, lowering the inspiratory drive to reduce V_T, adjusting PEEP to improve compliance, or even converting to controlled mechanical ventilation). Although this underscores the clinical relevance, it may also explain the relatively low values of plateau pressure and driving pressure reported, and it is uncertain whether the associations would hold with higher pressure levels (although it seems probable that higher values would reflect more injurious ventilator management, and yield stronger associations with adverse outcome). All the measurement were obtained during pressure support ventilation; although measurement of plateau pressure should be possible with other assisted ventilation modes,[24] this remains uncertain. Nonetheless, pressure support ventilation is the most common form of assisted ventilation in use.[30]

Confounding is possible when variables are colinear. Increased driving pressure and decreased respiratory system compliance were independently associated with mortality, thus it is not possible to determine whether elevated driving pressure has a causal role in increasing mortality or is simply a marker for greater severity of disease. Finally, some ventilator models do not permit an inspiratory hold during pressure support ventilation.

In conclusion, plateau pressure, driving pressure, and respiratory system compliance can be measured at the bedside during spontaneous ventilation, and both higher driving pressure and lower compliance are correlated with mortality. These findings, which do not necessarily imply causality, are biologically plausible, and if prospectively confirmed, driving pressure might be a useful management target during assisted ventilation.

Acknowledgments

We are indebted to Silvia Villa, Martina Viganò, M.D., Chiara Cunsolo, M.D., Melisa Juliana Polo Friz, M.D., Gabriele Valsecchi, M.D. and Davide Celsi, M.D. (University of Milan-Bicocca, Monza, Italy) for assistance in data extraction from electronic Medical records; Fabiana Madotto, Ph.D. (University of Milan-Bicocca, Monza, Italy) for statistical advice; and Alfio Bronco, M.D. (San Gerardo Hospital, Monza, Italy) for assistance in computed tomography scan analysis. This work would not have been possible without the daily work of all the medical staff of the General Intensive Care Unit of San Gerardo Hospital. This article is dedicated to the memory of Brian P. Kavanagh, M.B., a kind and humble person, a visionary scientist, and a passionate mentor. His contributions to this work and to the entire field of critical care medicine were invaluable.

Research Support

Support was provided solely from institutional and/or departmental sources. Dr. Kavanagh is supported by research funding from the Canadian Institutes of Health Research (Ottawa, Ontario, Canada) and holds the Dr. Geoffrey Barker Chair in Critical Care Research.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Bellani: University of Milan-Bicocca, Department of Medicine and Surgery, Via Cadore 48, Monza (MB), Italy. giacomo.bellani1@unimib.it. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

The Appearance and Disappearance of Dr. Edwin J. Thompson, Lynn's Celebrated Administrator of Nitrous Oxide

In 1879, I. A. Collins glued a copy of his cabinet photograph (*upper*) of a dental office in Lynn, Massachusetts, to an advertising card for dentist Edwin J. Thompson (ca. 1842 to 1912). Above the firm of Alfred Cross & Co., Clothiers, the dentist placed signage in the second-floor bay windows reading, "Teeth Extracted with Nitrous Oxide Gas" (*lower left*) by "Dr. Thompson Dentist" (*lower middle*). Through the open flanking window (*lower right*), photographer Collins may have captured the fleeting appearances of Dr. Thompson himself and an assistant gazing through the glazing. In 1912, the citizens of Lynn gazed one last time at Dr. Thompson before the then 70-yr-old dentist disappeared while fishing for salmon in Newfoundland. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.