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High Airway Occlusion Pressure Is Associated with Dyspnea and Increased Mortality in Critically Ill Mechanically Ventilated Patients

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Keywords:

P0.1; dyspnea; mechanical ventilation; mortality; weaning.

Author Contributions:

J.L.M., T.S., and A.D. designed the study. J.L.M., T.S., and A.D. coordinated the study. J.L.M., M.D., M.S., J.-D.R., S.J., E.A., M.F., S.H., A.M., and A.D. were responsible for = patient screening, enrollment, and follow-up. J.L.M., D.H., I.L., T.S., and A.D. analyzed the data. J.L.M., D.H., I.L., T.S., and A.D. wrote the manuscript. All authors had full access to all of the study data, contributed to draft the manuscript or revised it critically for important intellectual content, approved the final version of the manuscript, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Abstract

Rationale: Airway occlusion pressure at 100 ms (P0.1) reflects central respiratory drive. **Objectives:** We aimed to assess factors associated with P0.1 and whether an abnormally low or high P0.1 value is associated with higher mortality and longer duration of mechanical ventilation (MV). **Methods:** We performed a secondary analysis of a prospective cohort study conducted in 10 ICUs in France to evaluate dyspnea in communicative MV patients. In patients intubated for more than 24 hours, P0.1 was measured with dyspnea as soon as patients could communicate and the next day. **Measurements and Main Results:** Among 260 patients assessed after a median time of ventilation of 4 days, P0.1 was 1.9 (1-3.5) cm H₂O at enrollment, 24% had P0.1 values >3.5 cm H₂O, 37% had P0.1 values between 1.5 and 3.5 cm H₂O, and 39% had P0.1 values <1.5 cm H₂O. In multivariable linear regression, independent factors associated with P0.1 were the presence of dyspnea ($P = 0.037$), respiratory rate ($P < 0.001$), and PaO₂ ($P = 0.008$). Ninety-day mortality was 33% in patients with P0.1 > 3.5 cm H₂O versus 19% in those with P0.1 between 1.5 and 3.5 cm H₂O and 17% in those with P0.1 < 1.5 cm H₂O ($P = 0.046$). After adjustment for the main risk factors, P0.1 was associated with 90-day mortality (hazard ratio per 1 cm H₂O, 1.19 [95% confidence interval, 1.04-1.37]; $P = 0.011$). P0.1 was also independently associated with a longer duration of MV (hazard ratio per 1 cm H₂O, 1.10 [95% confidence interval, 1.02-1.19]; $P = 0.016$). **Conclusions:** In patients receiving invasive MV, abnormally high P0.1 values may suggest dyspnea and are associated with higher mortality and prolonged duration of MV.

Airway occlusion pressure at 100ms (P0.1) is defined as the decrease in airway pressure generated by the inspiratory muscles 100ms after the onset of inspiration against an occluded airway (1, 2). It is assumed that P0.1 is a reliable measure of the central respiratory drive (1, 3, 4), although this relationship can be affected by inspiratory muscle weakness. Measurement of P0.1 is currently available on most modern ventilators (5, 6) and is a simple and noninvasive tool to assess respiratory drive at the bedside in mechanically ventilated patients in the ICU.

A core of data in mechanically ventilated patients suggests that abnormal P0.1, and hence abnormal respiratory drive, might be associated with a worse outcome (7, 8). First, abnormally high or low respiratory drive is a marker of disease severity, as it may result from severe pulmonary disease, metabolic disorders, or damaged central respiratory centers after brain stem injury (9). Second, abnormally low or high respiratory drive may cause harm. On the one hand, abnormally low respiratory drive means low inspiratory effort, which in turn may cause diaphragm weakness (10) and compromised weaning success (11). On the other hand, abnormally high respiratory drive translates into high inspiratory effort, which may cause lung injury (12) and patient–ventilator asynchrony (13). Third, high respiratory drive may help detect symptoms that it parallels but that are often invisible. This is the case for dyspnea, the abnormal and distressing awareness of breathing, which is one of the most distressing experiences mechanically ventilated patients can endure (14). Because dyspnea increases when respiratory drive increases (15), P0.1 might be a useful tool to detect dyspnea.

In the present secondary analysis of a multicenter cohort study that evaluated dyspnea in communicative mechanically ventilated patients (16), our primary objective was to assess whether P0.1 was associated with dyspnea in this particular context. Our secondary objective was to evaluate the association between abnormal P0.1 and “hard” outcomes, namely, mortality and the duration of mechanical ventilation.

Methods

The study population was selected from patients included in the DyStress prospective observational cohort study conducted in France over a 28-month period (January 2016 to April 2018) in 10 ICUs belonging to the REVA (Réseau Européen de Recherche en Ventilation Artificielle) Network (16). The study was approved by the Institutional Review Board (CPP Ile de France VI 146- 13/A-01374-41). All patients or their relatives provided written informed consent to participate. The study complied with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (17).

Study Population

During the study period, investigators in each participating ICU screened patients for inclusion in the study daily between 9 and 12 A.M. Inclusion criteria were 1) invasive mechanical ventilation for more than 24 hours and 2) an estimated remaining ICU stay of more than 24 hours. Patients were included as soon as they were able to communicate with clinical staff members, with self-reported dyspnea being the primary outcome of the parent study. Exclusion criteria were 1) inability to communicate verbally and reliably (Richmond Agitation- Sedation Scale score-less than 22 or greater than 12, delirium according to the Confusion Assessment Method for the ICU, severe cognitive impairment or severe mental illness, inability to speak French, and severe hearing loss) and 2) age less than 18 years.

Data Collection and Study Design

Demographic data and medical history data, the cause of acute respiratory failure, and the duration of mechanical ventilation at the time of enrollment were collected. Data were collected between 9 and 12 A.M. Physiological data, blood gases, and ventilator settings were recorded. Dyspnea was searched for and quantified. Patients were first asked, “Do you have trouble breathing”? If the answer was yes, they were then asked to rate the intensity of their discomfort by placing a cursor on a 10-cm visual analog scale bounded on the left by “no respiratory discomfort” and on the right by “worst imaginable respiratory discomfort.” Anxiety was also measured using a 10-cm visual analog scale. P_{0.1} was assessed on the day of enrollment and on the next day if the patient was still intubated. P_{0.1} was recorded from the ventilator screen (either a single random measurement or the average of multiple measurements). The technique used to measure or estimate P_{0.1} depended on the brand of the ventilator (5, 6).

The presence of ICU-related adverse events was recorded daily: respiratory events (ICU-acquired pneumonia, pneumothorax, pulmonary embolism, or atelectasis), non-respiratory infection, acute hemorrhage, need for surgery, and cardiovascular events (ventricular or supraventricular arrhythmia, acute coronary syndrome, and any type of shock). The duration of mechanical ventilation; 28-, 60-, and 90-day mortality; length of ICU stay; and length of hospital stay were also collected.

Statistical Analysis

Statistical analysis was performed using R version R.4.1.3 (<https://www.r-project.org>). Medians and interquartile ranges are reported for continuous variables, and absolute and relative frequencies are reported for categorical variables.

P_{0.1} on the day of enrollment was used to stratify three groups of patients on the basis of the cutoffs of 1.5 and 3.5 cmH₂O that might define low and high respiratory drive, respectively, in mechanically ventilated patients according to previous reports (6, 18–20). Briefly, in healthy subjects, P_{0.1} varies from 0.5 to 1.5 cmH₂O (1, 6), and in intubated patients with chronic obstructive disease, P_{0.1} can vary from 2.5 to 5 cm H₂O (21). Recent data show that P_{0.1} in critically ill mechanically ventilated patients may range from 0 to 13 cm H₂O (2, 6, 22, 23). We chose these cutoffs on the basis of previous data showing that they were well correlated with insufficient and excessive inspiratory efforts measured using other methods (6, 18–20, 24, 25).

Each potential factor associated with P_{0.1} on the day of enrollment was then evaluated in a univariate analysis using the Kruskal-Wallis test for continuous variables and the chi-square or Fisher exact test for categorical variables. Among patients who reported dyspnea, the correlation between P_{0.1} and the intensity of dyspnea was assessed using the Spearman correlation coefficient.

P_{0.1} on the day of enrollment was also analyzed as a continuous variable, and univariate linear regression models were used to identify factors associated with P_{0.1}. The linearity of the association was checked graphically for quantitative factors. Multivariate analysis was then performed using a multivariable linear regression model, taking into account all potential

factors associated with P0.1 according to current knowledge (age, Sequential Organ Failure Assessment [SOFA] score, Richmond Agitation-Sedation Scale score, presence of dyspnea, presence of anxiety, respiratory rate, PaO₂, and pH).

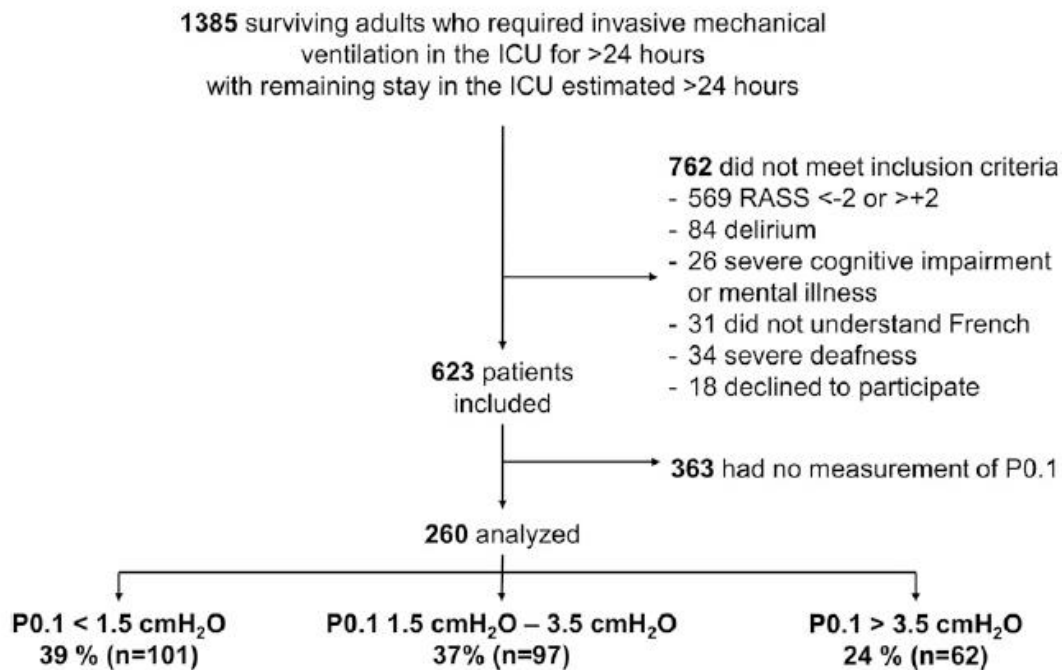


Figure 1. Study flowchart. P0.1 = airway occlusion pressure at 100 ms; RASS = Richmond Agitation-Sedation Scale.

The association between groups of P0.1 patients and the remaining duration of mechanical ventilation and 90-day mortality was described using the Kaplan-Meier method and compared using the log-rank test. Then, mixed-effects Cox proportional hazards regression models were used, taking into account potential risk factors for mortality and the remaining duration of mechanical ventilation (Charlson score, PaO₂:FIO₂ ratio, SOFA score, systolic blood pressure, and time from onset of invasive mechanical ventilation) and center to assess whether P0.1 was independently associated with the remaining duration of mechanical ventilation (from enrollment) and 90-day mortality. Adjusted predicted survival probability at Day 90 according to P0.1 (continuous) was computed from the multivariable Cox model and plotted. Log linearity was checked for all quantitative variables, graphically using deviance residuals, and using likelihood ratio tests for polynomial terms (two and three degrees).

The variance inflation factor was used to examine covariates for collinearity, and all variance inflation factors were less than 1.5. An interaction test was performed to detect the heterogeneity of the effect of P0.1 (>3.5 or <3.5 cmH₂O) between patients with and those without dyspnea. The variation of P0.1 from the day of enrollment to the next day (10% increase, 10% decrease, or variation, 10%) was described among patients for whom two measurements were available. The association between the variation of P0.1 and the remaining duration of mechanical ventilation and 90-day mortality was assessed using the same methods as those described above.

Table 1. Characteristics of the Study Population: Univariate Analysis

	All Patients (n=260)	P0.1 as a Categorical Variable			P Value	P0.1 as a Quantitative Variable	
		P0.1 < 1.5 cm H ₂ O (n=101)	P0.1 1.5–3.5 cm H ₂ O (n=97)	P0.1 > 3.5 cm H ₂ O (n=62)		Linear Regression Coefficient ± SE	P Value
Age, yr	64 (54–72)	67 (55–74)	65 (54–73)	60 (51–69)	0.1	–0.015 ± 0.008	0.068
Male gender	164 (63)	67 (66)	58 (60)	39 (63)	0.634	0.172 ± 0.249	0.489
BMI, kg/m ²	26 (22.5–30.5)	25.7 (21.6–30.5)	26.5 (23.2–30.4)	27 (22.6–31.3)	0.361	0.008 ± 0.016	0.603
Chronic respiratory disease	61 (23)	14 (14)	27 (28)	20 (32)	0.012	0.64 ± 0.281	0.023
Chronic heart disease	54 (21)	19 (19)	22 (23)	13 (21)	0.798	0.07 ± 0.296	0.814
Charlson score	4 (3–6)	4 (3–6)	4 (3–6)	4 (2–5)	0.331	–0.046 ± 0.048	0.331
SAPS 2 on ICU admission	49 (37–63)	50 (40–61)	49 (37–62)	46 (33–64)	0.491	–0.002 ± 0.007	0.789
Cause of ARF					0.245		
Acute-on-chronic ARF	27 (10)	8 (8)	14 (14)	5 (8)	—	Reference	—
Acute cardiogenic pulmonary edema	38 (15)	11 (11)	19 (20)	8 (13)	—	0.145 ± 0.488	0.767
Coma	34 (13)	17 (17)	9 (9)	8 (13)	—	0.025 ± 0.5	0.96
De novo ARF	77 (30)	36 (36)	26 (27)	15 (24)	—	0.001 ± 0.434	0.999
Sepsis, septic shock	30 (12)	7 (7)	12 (12)	11 (18)	—	0.62 ± 0.515	0.229
Postoperative	13 (5)	3 (3)	6 (6)	4 (6)	—	0.945 ± 0.655	0.151
Other	40 (15)	18 (18)	11 (11)	11 (18)	—	0.261 ± 0.504	0.604
Time from onset of invasive mechanical ventilation to enrollment, d	4 (2–9)	5 (2–11)	4 (2–9)	4.5 (2–7)	0.837	–0.012 ± 0.014	0.394

Definition of abbreviations: ARF = acute respiratory failure; BMI = body mass index; P0.1 = airway occlusion pressure at 100 ms; SAPS 2 = Simplified Acute Physiology Score 2. Quantitative variables are expressed as median (interquartile range). Qualitative variables are expressed as n (%).

Results

Study Population

A total of 1,385 patients required invasive mechanical ventilation for acute respiratory failure for more than 24 hours and had a remaining time in the ICU of more than 24 hours (Figure 1). Of these patients, 762 did not meet the inclusion criteria, and P0.1 on the day of enrollment was not measured in 363 patients, resulting in the inclusion of 260 patients. Among the 10 centers that participated in the parent study, P0.1 was not measured at all at 3 centers. In the seven remaining centers, P0.1 was measured in 30–100% of patients (see Table E1 in the online supplement, which also provides the proportions of ventilator brands used to measure P0.1 at each center). Patients were enrolled after a median time of 4 days of mechanical ventilation. Table E2 compares the characteristics of patients who had P0.1 measurements with those of patients in whom P0.1 was not measured. Patients in whom P0.1 was measured were more likely to have chronic heart disease, were more frequently admitted for acute on chronic respiratory failure, and had lower PaO₂ and higher PaCO₂.

Factors Associated with P0.1

At enrollment, median P0.1 was 1.9 (1–3.5) cm H₂O; 101 (39%) patients had P0.1 values < 1.5 cm H₂O, 97 (37%) had P0.1 values between 1.5 and 3.5 cmH₂O, and 62 (24%) had P0.1 values > 3.5 cmH₂O.

Demographic variables, body mass index, and Simplified Acute Physiology Score 2 on ICU admission were not associated with P0.1 on the day of enrollment, whereas underlying chronic respiratory disease was associated with higher P0.1 (Table 1). Dyspnea, anxiety, high respiratory rate, low PaO₂, high respiratory ratio (but not PaCO₂), VT, and low pressure support were associated with higher P0.1 (Table 2).

Multivariable linear regression analysis (see Table E3) showed that three factors were independently associated with P0.1 on the day of enrollment: dyspnea (coefficient estimate +/- SE, 0.588 +/- 0.279; P=0.037), respiratory rate (estimate +/- SE, 0.076 +/- 0.018; P,0.001), and PaO₂ (estimate +/- SE, 20.010 +/- 0.004; P= 0.008). When ventilatory ratio was added to the model, three factors were independently associated with P0.1 on the day of enrollment:

respiratory rate (estimate +/-SE, 0.053 +/- 0.021; P=0.012), PaO2 (estimate +/- SE, 20.008 +/- 0.004; P= 0.035), and ventilatory ratio (estimate +/- SE, 0.474 +/- 0.226; P=0.037).

Table 2. Characteristics of the Patients at Enrollment: Univariate Analysis

	All Patients (n = 260)	P0.1 as a Categorical Variable			P Value	P0.1 as a Quantitative Variable	
		P0.1 <1.5 cm H ₂ O (n = 101)	P0.1 1.5 to 3.5 cm H ₂ O (n = 97)	P0.1 >3.5 cm H ₂ O (n = 62)		Linear Regression Coefficient ± SE	P Value
Anxiety, yes	110 (42)	36 (36)	42 (43)	32 (52)	0.129	0.476 ± 0.241	0.05
SOFA score	4 (2 to 7)	4 (2 to 6)	5 (2 to 7)	4 (3 to 7)	0.573	0.034 ± 0.041	0.415
RASS score	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0.064	-0.096 ± 0.31	0.756
Dyspnea, yes	94 (36)	26 (26)	37 (38)	31 (50)	0.007	0.726 ± 0.246	0.003
Respiratory rate, breaths/min	23 (19 to 27)	21 (18 to 24)	24 (19 to 29)	25 (19 to 29)	<0.0001	0.067 ± 0.018	<0.001
Systolic blood pressure, mmHg	132 (114 to 145)	125 (113 to 143)	135 (118 to 147)	131 (111 to 145)	0.501	0.005 ± 0.005	0.395
Heart rate, beats/min	95 (79 to 108)	92 (76 to 106)	97 (79 to 110)	95 (84 to 113)	0.084	0.01 ± 0.006	0.098
Temperature, °C	37.2 (36.7 to 37.7)	37.3 (36.7 to 37.7)	37.2 (36.8 to 37.7)	37.1 (36.6 to 37.6)	0.591	-0.092 ± 0.159	0.561
Arterial blood gases							
PaO ₂ , mmHg	91 (76 to 110)	96 (78 to 116)	90 (74 to 103)	88 (73 to 106)	0.077	-0.01 ± 0.003	0.006
PaCO ₂ , mmHg	38 (34 to 42)	38 (35 to 43)	37 (33 to 42)	38 (34 to 44)	0.652	0.016 ± 0.016	0.319
pH	7.46 (7.4 to 7.49)	7.46 (7.4 to 7.48)	7.47 (7.42 to 7.49)	7.44 (7.4 to 7.48)	0.070	-0.467 ± 1.879	0.804
HCO ₃ , mmol/L	26 (23 to 30)	26 (23 to 29)	26 (24 to 30)	26 (21 to 30)	0.555	0.016 ± 0.022	0.46
Hb, g/dl	10 (8.7 to 11.5)	9.9 (8.4 to 11.2)	10.4 (8.9 to 12)	9.8 (8.3 to 10.9)	0.122	-0.038 ± 0.057	0.505
Ventilatory ratio*	1.7 (1.3 to 2.1)	1.5 (1.2 to 1.9)	1.7 (1.4 to 2.0)	1.9 (1.5 to 2.2)	0.001	0.927 ± 0.174	<0.001
Base excess, mmol/L	2.6 (-0.9 to 6.9)	2.0 (-0.9 to 5.5)	3.2 (0.1 to 7.7)	2.1 (-2.2 to 6.4)	0.331	0.011 ± 0.02	0.578
Ventilator settings							
Ventilator mode					0.956		
Volume assist-control ventilation	31 (12)	12 (12)	12 (12)	7 (11)		Reference	—
Pressure support ventilation	226 (87)	87 (86)	84 (87)	55 (89)		0.337 ± 0.371	0.364
Positive end-expiratory pressure, cm H ₂ O	5 (5 to 8)	5 (5 to 7)	5 (5 to 7)	6 (5 to 8)	0.211	0.111 ± 0.066	0.092
Measured V _T , ml	460 (400 to 540)	483 (415 to 528)	440 (371 to 534)	466 (409 to 593)	0.186	0.002 ± 0.001	0.041
Pressure support†, cm H ₂ O	10 (7 to 12)	10 (8 to 12)	10 (7 to 12)	10 (7 to 12)	0.297	-0.08 ± 0.041	0.052
Analgesic or sedative drugs					0.855		0.343
Opioids	90 (35)	30 (30)	37 (38)	23 (37)	0.41	0.444 ± 0.202	0.029
Benzodiazepines	30 (12)	14 (14)	11 (11)	5 (8)	0.53	-0.624 ± 0.286	0.03
Propofol	65 (25)	23 (23)	25 (26)	17 (27)	0.78	0.293 ± 0.211	0.165

Definition of abbreviations: P0.1 = airway occlusion pressure at 100 ms; RASS = Richmond Agitation-Sedation Scale; SOFA = Sequential Organ Failure Assessment. Quantitative variables are expressed as median (interquartile range). Qualitative variables are expressed as n (%).
*Ventilatory ratio is defined as (measured V_T × respiratory rate × PaCO₂)/(predicted body weight × 100 × 37.5).
†In the 226 patients on pressure support ventilation.

The sensitivity of a P0.1 value.3.5 cm H₂O to detect dyspnea was 0.33, specificity was 0.81, positive predictive value was 0.5, and negative predictive value was 0.68. Among patients who reported dyspnea, the correlation between P0.1 and the intensity of dyspnea was not significant (rho = 0.13 [95% confidence interval (CI), - 0.08 to 0.32]) (see Figure E1).

Table 3. Outcomes According to Airway Occlusion Pressure at 100 ms

	All Patients (n = 260)	P0.1 <1.5 cm H ₂ O (n = 101)	P0.1 1.5–3.5 cm H ₂ O (n = 97)	P0.1 >3.5 cm H ₂ O (n = 62)	P Value
Remaining duration of mechanical ventilation, d	6 (3–12)	6 (3–10)	6 (3–14)	7 (4–13)	0.119
28-d mortality	35 (13)	10 (10)	10 (10)	15 (24)	0.019
60-d mortality	44 (17)	13 (13)	12 (13)	19 (31)	0.004
90-d mortality*	55 (21)	17 (17)	18 (19)	20 (33)	0.046
Length of ICU stay, d	11 (7–21)	10 (6–20)	12 (7–21)	11 (8–22)	0.347
Length of hospital stay, d	28 (17–50)	26 (17–41)	28 (15–52)	35 (18–64)	0.247
At least one ICU-acquired adverse event	65 (25)	22 (22)	26 (27)	17 (27)	0.613

Definition of abbreviation: P0.1 = airway occlusion pressure at 100 ms. Quantitative variables are expressed as median (interquartile range). Qualitative variables are expressed as n (%).
*Available in 256 patients.

Of note, among the 90 patients who received opioids, 52 (10%) received sufentanil, 8 (9%) received fentanyl, 8 (8%) received opioids, and 22 (24%) received tramadol. The cumulative dose of opioids received during the first 24 hours did not differ according to P0.1

Mortality and Remaining Duration of Mechanical Ventilation

Higher P0.1 at enrollment was associated with higher 28-, 60-, and 90-day mortality (Table 3). The cumulative probability of survival up to 90 days after enrollment differed according to P0.1 group (P=0.03, log-rank test; Figure 2A). Patients with P0.1>3.5 cm H₂O at enrollment

had a lower probability of survival than those with $P0.1 < 1.5$ cm H₂O (hazard ratio [HR], 1.84 [95% CI, 1.07–3.17]) or between 1.5 and 3.5 cmH₂O (HR, 1.85 [95% CI, 1.08–3.19]). There was no significant difference between patients with $P0.1 < 1.5$ cmH₂O and those with $P0.1$ between 1.5 and 3.5 cmH₂O (HR, 0.78 [95% CI, 0.45–1.34]). Table E4 describes factors associated with 90-day mortality by univariate analysis. In the multivariable Cox regression model, two factors were associated with 90-day mortality: $P0.1$ (HR, 1.18 [95% CI, 1.021–1.36]; $P=0.023$) and time from the onset of invasive mechanical ventilation to enrollment (HR, 0.94 [95% CI, 0.89–0.99]; $P = 0.045$) (see Table E5). Figure 2B shows the adjusted predicted survival probability at Day 90 according to $P0.1$ value (continuous) computed from the multivariable Cox model. No significant interaction was noted between $P0.1$ (>3.5 or <3.5 cmH₂O) and the concomitant presence or absence of dyspnea (P for interaction = 0.76).

The cumulative probability of being separated from the ventilator differed according to $P0.1$ ($P = 0.03$, log-rank test; Figure 3). Patients with $P0.1 > 3.5$ cmH₂O at enrollment had a lower probability of being separated from the ventilator than patients with $P0.1 < 1.5$ cmH₂O (HR, 0.69 [95% CI, 0.5–0.95]) or between 1.5 and 3.5 cmH₂O (HR, 0.7 [95% CI, 0.52–0.96]). There was no significant difference between patients with $P0.1 < 1.5$ cmH₂O and those with $P0.1$ between 1.5 and 3.5 cmH₂O (HR, 1.03 [95% CI, 0.75–1.42]). Table E6 shows factors associated with the remaining duration of mechanical ventilation by univariate analysis.

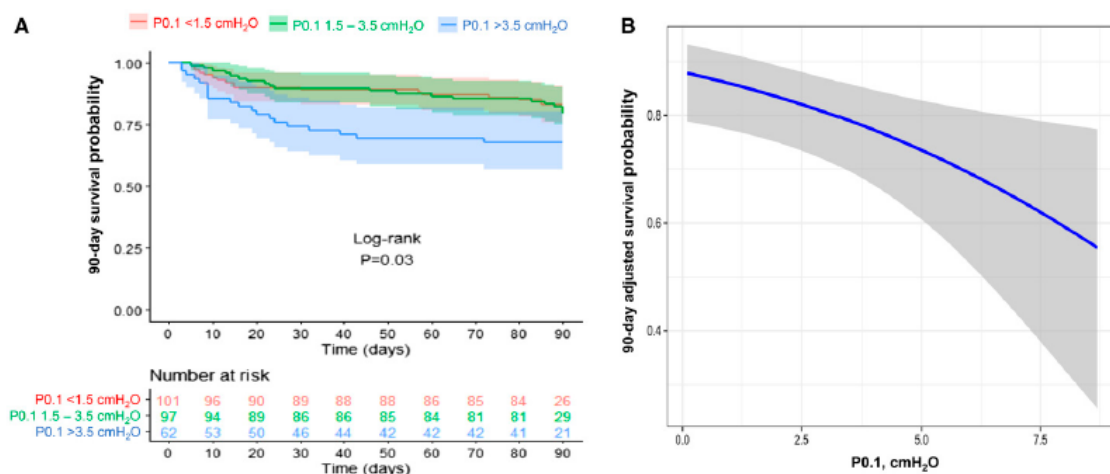


Figure 2. (A and B) Kaplan-Meier estimates of probability of 90-day mortality (A) and adjusted predicted survival probability at Day 90 according to $P0.1$ (continuous) computed from the multivariable Cox model (B). $P0.1$ = airway occlusion pressure at 100 ms.

By multivariate analysis, $P0.1$ was the only factor associated with a longer remaining duration of mechanical ventilation (HR, 1.11 [95% CI, 1.01–1.22 [$P=0.024$]]) (see Table E7).

The probability to develop at least one ICU-related adverse events did not differ according to $P0.1$ (Table 3 and E8).

Course of $P0.1$ between the Two Measurements

Median $P0.1$ on the day after enrollment (measured in 125 patients) was 1.9 (1 to 3.1) cm H₂O. The difference in $P0.1$ between enrollment and the next day was 0 (20.7 to 0.6) cmH₂O. Between enrollment and the next day, $P0.1$ increased by more than 10% in 47 patients (38%), decreased by more than 10% in 54 patients (43%), and changed by less than 10% in the 24 remaining patients (19%). In the meantime, the proportion of patients receiving propofol did not change (20% [$n=25$]; $P = 0.278$), the proportion of patients receiving benzodiazepines

decreased (22% [n=28]; P = 0.005), and the proportion of patients receiving opioids increased (51% [n=64]; P=0.002). The dose of opioids patients received did not differ between the two days. Changes in P0.1 between enrollment and the next day were not associated with any difference in terms of mortality and remaining duration of mechanical ventilation.

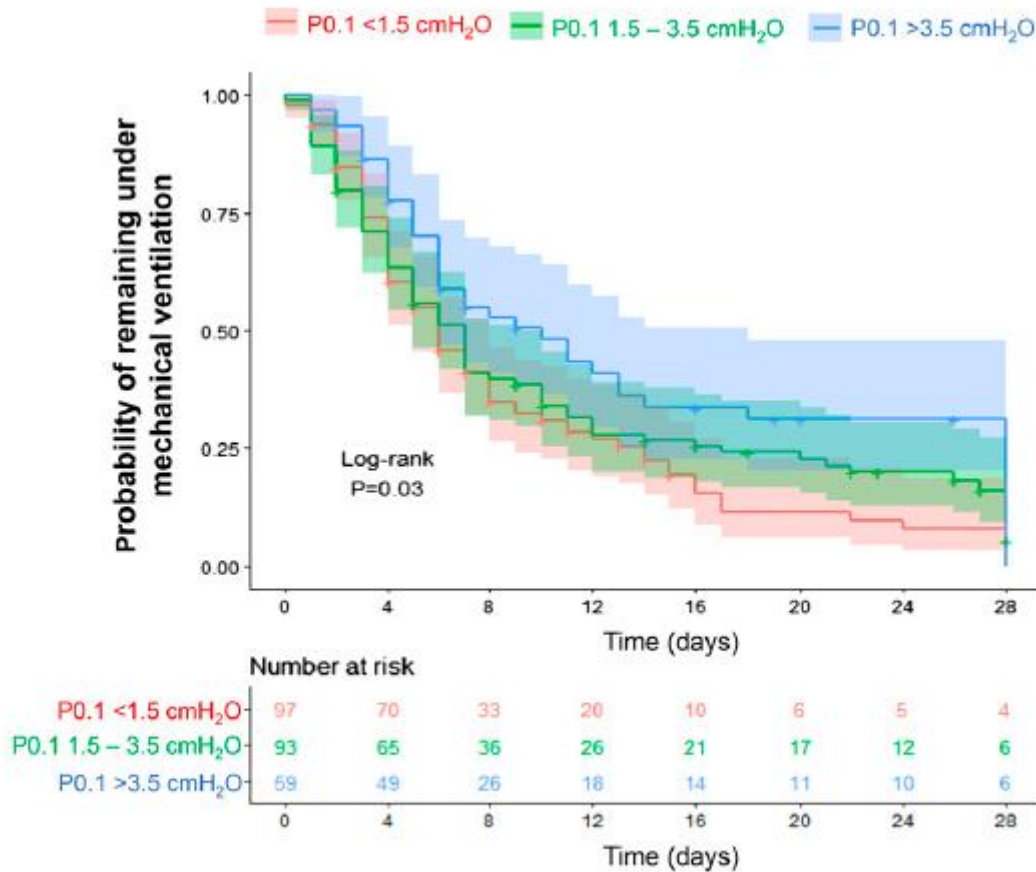


Figure 3. Kaplan-Meier estimates of probability of weaning from mechanical ventilation at Day 28 according to P0.1. P0.1 = airway occlusion pressure at 100 ms.

Discussion

The main and major findings of our study in a cohort of intubated patients recovering from acute respiratory failure are that 1) high P0.1 was associated with the presence of dyspnea, and 2) high P0.1 was independently associated with a worse outcome, namely, a higher mortality rate and a longer duration of mechanical ventilation.

Defined as a subjective experience of breathing discomfort (26), dyspnea affects 35–50% of intubated patients (16, 27). Dyspnea is not only an immediate cause of suffering and anxiety, it is also associated with more difficult weaning (27), with negative memories of ICU stays (28, 29), and with a higher risk of developing post-traumatic stress disorder (16). Relieving dyspnea has become a major matter of concern in ICU patients. As dyspnea is a self-reported symptom, patients need to be fully communicative to report it, as was the case in our study. However, in the ICU, many patients cannot communicate for a variety of reasons, such as the intubation probe itself, sedation, or delirium. However, non-communicative patients may also experience dyspnea and its devastating consequences but are not able to report it.

Unfortunately, it is well known that clinical staff members underestimate dyspnea in mechanically ventilated patients (14, 30–32). For this reason, our team and others have developed hetero evaluation scales to detect dyspnea in non-communicative patients, such as the Mechanical Ventilation–Respiratory Distress Observation Scale (33–36). However, the performance of these scales remains limited (33–36). Elevated respiratory drive, a consequence of respiratory system load capacity imbalance, is one of the mechanisms that may cause dyspnea (15). As P0.1 is a surrogate of respiratory drive, the association between P0.1 and dyspnea we observe is not unexpected, and previous reports have shown a correlation between dyspnea and P0.1 in patients with chronic respiratory diseases (37–39). Of note, the sensitivity and positive predictive value of elevated P0.1 to detect dyspnea were poor to moderate, whereas the specificity and negative predictive value were moderate to high. Our results pave the way of future studies evaluating how P0.1 could improve the performance of hetero evaluation scales to detect dyspnea in non-communicative patients, such as the Mechanical Ventilation–Respiratory Distress Observation Scale (33–36). Surprisingly, we did not observe the association between P0.1 and PaCO₂ that previous investigators found (9). However, we found that an elevated P0.1 was associated with a high respiratory ratio, a marker of decreased ventilator efficiency (40, 41). Finally, we confirmed the significant relationship between PaO₂ and P0.1 (9, 42).

We also showed an independent association between elevated P0.1 and the duration of mechanical ventilation. To wean a patient from mechanical ventilation, respiratory system loading should not exceed the capacity of respiratory muscles. In case of load capacity imbalance, weaning is not possible. Load capacity imbalance increases respiratory drive and hence P0.1 (22).

Previous studies have evaluated the predictive value of P0.1 on successful weaning from mechanical ventilation, assuming that separation from the ventilator could not be possible in case of elevated P0.1 (7, 8). These studies have shown that an elevated P0.1 was associated with a higher risk of weaning failure (7, 8). This ventilator dependency of patients with a high P0.1 contributes to the association between high P0.1 and a longer duration of mechanical ventilation. More recently, it has been shown that in mechanically ventilated patients with acute respiratory distress syndrome due to coronavirus disease (COVID-19), high P0.1 was associated with a higher risk of relapse of respiratory failure during the weaning process, a possible consequence of patient self-inflicted lung injury resulting from a high respiratory drive (43). This may slow down the weaning process and hence contribute to increase the remaining duration of mechanical ventilation.

Finally, we showed an independent association between elevated P0.1 and mortality, suggesting potential deleterious consequences of abnormal respiratory drive. Indeed, in our study, the association between P0.1 and mortality remained significant after adjustment for SOFA score and PaO₂:FIO₂ ratio, two markers of critical illness severity (44). This may indicate that P0.1 could be not only a marker of severity of the critical illness but also a surrogate of a harmful high respiratory drive, which generates high inspiratory efforts, provided that there is no muscle weakness (45). In turn, these high inspiratory efforts may generate high transpulmonary pressure and subsequent lung injury (12), as well as patient–ventilator asynchrony (13). Of note, in our study, low P0.1 was not associated with a longer duration of mechanical ventilation, which was surprising, as low respiratory drive causes low inspiratory effort, which in turn may cause diaphragm atrophy (10) and hence have an adverse impact on weaning success (11). It is possible that the lower cutoff value we chose (1.5 cmH₂O) was not low enough to identify patients exposed to the clinical consequences of low

respiratory drive, even though this cutoff is consistent with values reported in the literature (6, 18–20, 24, 25). However, we cannot exclude that abnormally low P0.1 was caused by residual sedation, although a recent study did not demonstrate any statistical relationship between P0.1 and sedation (9).

Strengths of our study include the size of our cohort (among the largest reported), a design that is consistent with clinical practice (i.e., the use of the P0.1 displayed by the ventilator), and the fact that P0.1 is probably the easiest and fastest estimation of respiratory drive that can be performed at bedside.

Our study also has several limitations. First, the cutoffs chosen to define high and low P0.1 were based on a core of literature rather than on any standard definition (1, 2, 6, 18–25). Second, in our study, P0.1 was measured at bedside by the ventilator, which is an accurate reflection of the gold standard, even though it could vary according to ventilator model (5) and because of technical or patient-related reasons (6). We used P0.1 measurement by the ventilator rather than the gold standard because we wanted to study a bedside measurement of P0.1 that clinicians can use in their daily practice. Of note, many of the measurements were done on Draeger ventilators, which display a P0.1 value that has excellent precision and accuracy (6).

Third, P0.1 was not measured daily but only twice, so we could not describe changes in P0.1 over the entire duration of mechanical ventilation and the potential association between these changes in P0.1 and the outcome. Fourth, we did not measure respiratory muscle strength. As such, we cannot rule out that in some patients, severe respiratory muscle weakness may have caused an underestimation of P0.1 as a surrogate of respiratory drive. One should keep in mind that P0.1 as a measure of respiratory drive is not expected to be influenced by respiratory muscle weakness, but this was shown only up to a certain degree (3).

Fifth, we did not assess respiratory system mechanics, especially intrinsic positive end-inspiratory pressure. However, it has been shown that the measure of P0.1 is reliable in patients with various degrees of intrinsic positive end-inspiratory pressure (46). Sixth, P0.1 was measured on the first day the patient was able to communicate, which may vary among patients, and means that not all patients were studied after the same duration of mechanical ventilation. Therefore, we cannot exclude that the patients were at different stages of recovery from the initial insult. However, duration of mechanical ventilation before P0.1 assessment did not differ among the three groups. In addition, the ability to communicate is a key step in the recovery process, as it signals the return of function to supra-bulbar efferents, including cortical efferents. The involvement of the cortex in the drive to breathe is a factor that favors dyspnea in patients with chronic respiratory failure (47). Our results suggest that it might also be associated with a poorer prognosis. Obviously, future research on the relationship between P0.1 measured at different time points and outcomes is needed.

Finally, P0.1 was measured in 42% of patients, as it was not the primary goal of the trial (16). Although PaCO₂ was higher in patients in whom P0.1 was measured and those in whom P0.1 was not measured, pH, which is a major determinant of respiratory drive, was not different between the two groups.

Conclusions

High P0.1 should prompt caregivers to investigate for dyspnea in communicative mechanically ventilated patients. Our study also shows an association between high P0.1 and major outcomes such as the duration of mechanical ventilation and mortality. Further studies should investigate whether interventions deemed to normalize P0.1, for instance, adjusting ventilator settings or the posology of sedative agents, might improve patient outcomes.

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

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