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Failure of First Transition to Pressure Support Ventilation After Spontaneous Awakening Trials in Hypoxemic Respiratory Failure: Influence of COVID-19

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OBJECTIVES: To describe the rate of failure of the first transition to pressure support ventilation (PSV) after systematic spontaneous awakening trials (SATs) in patients with acute hypoxemic respiratory failure (AHRF) and to assess whether the failure is higher in COVID-19 compared with AHRF of other etiologies. To determine predictors and potential association of failure with outcomes.

DESIGN: Retrospective cohort study.

SETTING: Twenty-eight-bedded medical-surgical ICU in a private hospital (Argentina).

PATIENTS: Subjects with arterial pressure of oxygen (AHRF to F_{IO_2} [Pa_{O_2}/F_{IO_2}] < 300 mm Hg) of different etiologies under controlled mechanical ventilation (MV).

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We collected data during controlled ventilation within 24 hours before SAT followed by the first PSV transition. Failure was defined as the need to return to fully controlled MV within 3 calendar days of PSV start. A total of 274 patients with AHRF (189 COVID-19 and 85 non-COVID-19) were included. The failure occurred in 120 of 274 subjects (43.7%) and was higher in COVID-19 versus non-COVID-19 (49.7% and 30.5%; $p = 0.003$). COVID-19 diagnosis (odds ratio [OR]: 2.22; 95% CI [1.15–4.43]; $p = 0.020$), previous neuromuscular blockers (OR: 2.16; 95% CI [1.15–4.11]; $p = 0.017$) and higher fentanyl dose (OR: 1.29; 95% CI [1.05–1.60]; $p = 0.018$) increased the failure chances. Higher BMI (OR: 0.95; 95% CI [0.91–0.99]; $p = 0.029$), Pa_{O_2}/F_{IO_2} (OR: 0.87; 95% CI [0.78–0.97]; $p = 0.017$), and pH (OR: 0.61; 95% CI [0.38–0.96]; $p = 0.035$) were protective. Failure groups had higher 60-day ventilator dependence ($p < 0.001$), MV duration ($p < 0.0001$), and ICU stay ($p = 0.001$). Patients who failed had higher mortality in COVID-19 group ($p < 0.001$) but not in the non-COVID-19 ($p = 0.083$).

CONCLUSIONS: In patients with AHRF of different etiologies, the failure of the first PSV attempt was 43.7%, and at a higher rate in COVID-19. Independent risk factors included COVID-19 diagnosis, fentanyl dose, previous neuromuscular blockers, acidosis and hypoxemia preceding SAT, whereas higher BMI was protective. Failure was associated with worse outcomes.

KEY WORDS: acute respiratory distress syndrome; assisted ventilation; mechanical ventilation; respiratory insufficiency; sedatives.

Patients with acute hypoxemic respiratory failure (AHRF) are commonly admitted to ICU and require invasive mechanical ventilation (MV) to maintain gas exchange and relieve work of breathing until the underlying disease has begun to resolve (1–4).

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KEY FINDINGS

Question: What is the rate of failure of the first pressure support ventilation (PSV) attempt, its predictors, and associated outcomes in acute hypoxemic respiratory failure (AHRF)?

Findings: Failure of the first PSV transition was 43.7%. Risk factors included COVID-19 diagnosis, higher fentanyl dose, neuromuscular blockers, acidosis, and hypoxemia, whereas higher BMI was protective. The failure was associated with poor outcomes.

Meaning: After awakening trials, failure of the first PSV transition in AHRF is frequent and is associated with worse outcomes. Patients' characteristics and severity markers may serve as predictors. Future studies are necessary to determine optimal clinical conditions for partially assisted ventilation.

Spontaneous Awakening Trials (SATs) allow for minimizing the negative effects of deep sedation on respiratory muscles by promoting assisted ventilation (5–7). However, spontaneous breathing may not be well tolerated in patients with previously injured lungs (8–10). Particularly for COVID-19, pressure support ventilation (PSV) has been shown to be challenging, with a high proportion of cases experiencing significant worsening (11, 12). Whether the failure of the first transition to assisted ventilation is higher in COVID-19 compared with AHRF of other etiologies has not yet been determined. Furthermore, its predictors and association with clinical outcomes are unknown.

We took benefit of a systematic use of SAT in our ICU to analyze mechanically ventilated patients with AHRF. Our main objective was to describe the rate of failure of the first transition to PSV and to assess whether the failure is higher in COVID-19 versus AHRF of other etiologies. We also aimed to determine its predictors and association with clinical outcomes.

MATERIALS AND METHODS

We conducted a retrospective cohort study from June 1, 2018, to September 30, 2022, in the ICU of Sanatorio Anchorena San Martín, Argentina. The study was carried out following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines recommendations (13).

Ethics Statement

The study was approved by the ethical review board of Eva Perón Hospital, Buenos Aires, Argentina (number: 12/22—approval date: February 22, 2021). The informed consent was waived due to the retrospective design. The study was performed in accordance with the 2008 Declaration of Helsinki and its later amendments.

Study Population

We considered eligible adults who fulfilled AHRF criteria (arterial pressure of oxygen to F_{IO_2} [P_{aO_2}/F_{IO_2}] < 300 mm Hg), required MV greater than 12 hours, and received controlled ventilation. We enrolled patients with SAT and PSV switches. We excluded patients with unplanned extubation, previous neuromuscular disease, and palliative care.

For the purpose of analysis, we divided patients into two groups: COVID-19 and non-COVID-19. The former was collected from 2020 to 2022. To have a sufficient number of non-COVID-19, the latter was retrieved from 2018 to 2022. During the study period, the regular staff of physicians, respiratory therapists, and nurses remained stable. Furthermore, two intensivists, two respiratory therapists, and four nurses were incorporated and trained during the pandemic to deal with the increasing demands. The protocols of sedation-analgesia, fluids management, and MV in our ICU were not altered in this period.

Procedure

We collected data from electronic-clinical records at two-time points during controlled ventilation: 1) at baseline, within 24 hours of intubation and 2) pre-SAT, within 24 hours before SAT followed by the first PSV transition (**Appendix 1**, http://links.lww.com/CCX/B244).

According to our ICU protocols, the patients were shortly assessed after intubation to determine a targeted sedation/analgesia strategy. The Richmond Agitation and Sedation Scale (RASS) was 0/–1 (14), unless one of the following: severe hypoxemia (P_{aO_2}/F_{IO_2} < 150 mm Hg); plateau pressure (Pplat) greater

than 30 cm H_2O or airway driving pressure greater than 15 cm H_2O after adjusting tidal volume (Vt) less than or equal to 6 mL/kg of predicted body weight, active seizures, recent myocardial ischemia, increased intracranial pressure, severe hemodynamic instability (noradrenaline ≥ 0.3 μg/kg/min or ≥ 2 vasoactive drugs to maintain mean arterial pressure ≥ 65 mm Hg). In these cases, a propofol and fentanyl-based sedation strategy was used to achieve RASS −4/−5. The management of neuromuscular blocking agents (NMBAs) and prone position was based on previous recommendations (**Appendix 2**, http://links.lww.com/CCX/B244 and **Appendix 3**, http://links.lww.com/CCX/B244) (15–17). Patients were ventilated in volume control following protective standards (18–20). When prone was no longer required, Pao_2/Fio_2 greater than 150 mm Hg in supine for greater than 6 hours without NMBAs, and noradrenaline less than 0.3 μg/kg/min, sedatives were interrupted and analgesics were reduced to achieve RASS −1/0. Negative fluid balance was prioritized to facilitate MV weaning. Once the patient was able to trigger the ventilator, we switched from volume control to PSV, and assisted ventilation was adjusted to individualized protective lung- and diaphragmatic targets (**Appendix 4**, http://links.lww.com/CCX/B244) (21). When the patient fulfilled weaning criteria (**Appendix 5**, http://links.lww.com/CCX/B244), a spontaneous breathing trial (SBT) was performed with pressure support 5 cm H_2O or T-tube for 30–120 minutes (22, 23). From March 2020 to March 2021, we did not use noninvasive support for COVID-19. From April 2021 onward, high-flow nasal cannula was implemented to avoid intubation (24). Noninvasive support was used to prevent reintubation in high-risk patients (25). Reintubation was considered according to predefined criteria (**Appendix 6**, http://links.lww.com/CCX/B244).

Definitions and Outcomes

Failure was defined as the need to return to fully controlled MV within 3 calendar days of starting the first transition to PSV. The calendar day that PSV started was considered "day 0." The decision to declare failure was based on judgment of the attending physicians. The main reasons for failure were retrospectively collected and grouped based on previous studies (**Appendix 7**, http://links.lww.com/CCX/B244) (8, 10, 12).

Our primary endpoint was the rate of failure of the first transition to PSV. In patients with more than one PSV switch, only the first was considered. Secondary endpoints were the proportion of extubations, tracheostomies, the 60-day ventilator-free days, MV duration, ICU length of stay, and ICU mortality.

The definitive discontinuation of MV was defined according to previous studies (22). Patients who died were considered to have 0 ventilator-free days. Patients were followed until ICU discharge or death.

Statistical Analysis

Continuous variables are reported as median (interquartile range [IQR] 25th–75th) or mean (SD), as appropriate. Categorical variables are reported as numbers (proportion). Continuous data were compared with the t-test or Wilcoxon-Mann-Whitney *U* test according to normality checked by the Shapiro-Wilk test. Categorical comparisons were performed by Chi-square or Fisher exact test, as appropriate.

A binomial logistic regression model was constructed to determine predictors of the failure of the first PSV transition and its association with COVID-19 diagnosis. The following predictors, all of them collected during controlled ventilation within 24 hours before SAT, were selected a priori and tested as continuous variables: normalized respiratory system elastance (26), Pao_2/Fio_2 (27), nonrespiratory Sequential Organ Failure Assessment (SOFA) (28) and pH (29). These variables represent the patient's clinical condition that supported the SAT decision. In addition, to account for the potential differences in sedation/analgesia management imposed by the pandemic (30), we introduced in the model the average dose of propofol, midazolam, and fentanyl received 24 hours before SAT. Likewise, COVID-19 diagnosis, previous requirements for NMBAs, and prone were tested as dichotomous variables. We adjusted for age, Acute Physiology and Chronic Health Disease Classification System (APACHE) II (31), BMI, and the total time of respiratory support (noninvasive + invasive) before assuming PSV. A stepwise backward selection method was used to build the final predictive model. The goodness-of-fit of the model was assessed by the Hosmer-Lemeshow test.

The Kaplan-Meier approach was used to estimate the probability of 60-day discontinuation of MV. The groups (PSV-failure vs PSV-success) were compared with the unadjusted Log-Rank test. Patients who died

before day 60 were censored. The remaining secondary outcomes were compared by Chi-square or Fisher exact test, and *t*-test or Wilcoxon-Mann-Whitney *U* test, as appropriate. Because of the potential type-I error due to multiple comparisons, findings of secondary endpoints should be interpreted as exploratory. Consequently, the results of these statistical comparisons must be considered hypothesis-generating.

A two-sided *p* value of less than or equal to 0.05 was considered statistically significant. Data were analyzed using R version 4.1.3 (www.r-project.org).

RESULTS

Between June 2018 and August 2022, 1,016 patients required invasive MV greater than 12 hours, of whom 418 fulfilled AHRF criteria during controlled MV. Of them, 144 (34.4%) were excluded mainly because an SAT was never performed (n = 117). All of these patients died in ICU, except for one who was transferred to another facility without SAT. Finally, 274 patients (189 COVID-19 and 85 non-COVID-19) were included (**Fig. 1**).

The patient's characteristics and sedatives used 24 hours before SAT are shown in **Table 1**. Patients with COVID-19-related AHRF had lower APACHE II and SOFA at admission. Furthermore, they fulfilled ARDS criteria more frequently and had a greater need for NMBAs and prone position. Patients with COVID-19 received a higher average dose of propofol 24 hours before the SAT followed by the first PSV attempt.

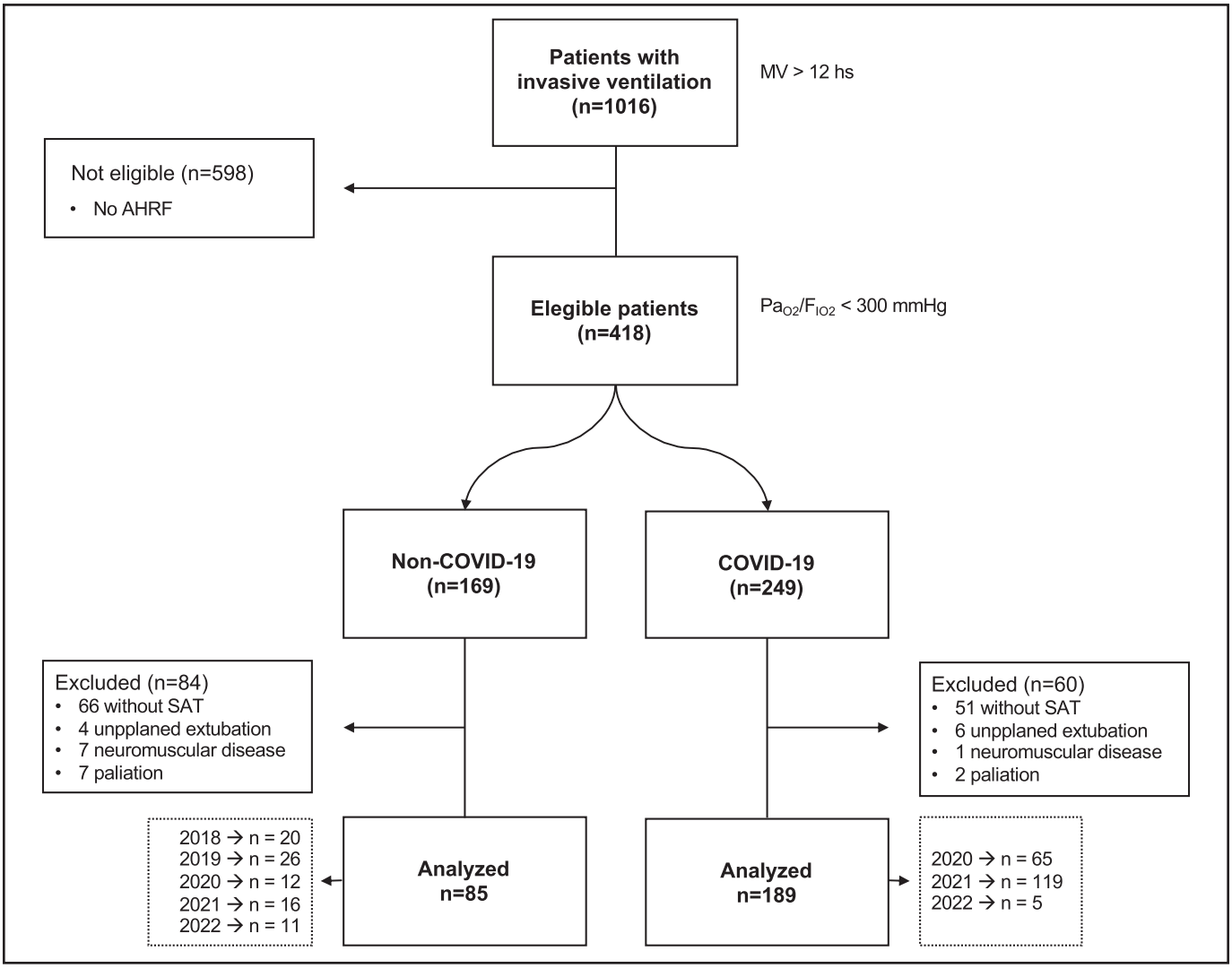

Figure 1. Flowchart of the patients. AHRF = acute hypoxemic respiratory failure, MV = mechanical ventilation, SAT = Spontaneous Awakening Trials.

TABLE 1.
Characteristics of the Patients and Sedatives Use

Demographic Characteristics at Admission	COVID-19 ($n = 189$)	Non-COVID-19 ($n = 85$)	p
Age, yr	58.0 (13.0)	57.0 (18.2)	0.920
Gender (female)	64 (34.0)	31 (36.4)	0.682
BMI, kg/m^2	32.0 (28.0–36.0)	28.3 (25.5–33.3)	< 0.0001
Acute Physiology and Chronic Health Disease Classification System II, points	12.0 (8.0–16.0)	18.0 (12.5–23.5)	< 0.0001
Sequential Organ Failure Assessment, points	6.0 (4.5–7.0)	7.0 (6.0–9.0)	< 0.0001
Hypertension, *n* (%)	66 (34.9)	34 (40.0)	0.419
Immunoression, *n* (%)	2 (1.1)	12 (14.1)	< 0.0001
Active cancer, *n* (%)	4 (2.1)	14 (16.4)	< 0.0001
Chronic lung disease, *n* (%)	9 (4.8)	13 (15.2)	0.006
Chronic cardiovascular disease, *n* (%)	18 (9.5)	13 (15.2)	0.316
Main cause of intubation, *n* (%)			
Pneumonia	189 (100.0)	39 (45.8)	< 0.0001
Shock	0 (0.0)	13 (15.2)	< 0.0001
Polytrauma	0 (0.0)	10 (11.7)	< 0.0001
Postoperative	0 (0.0)	8 (9.4)	< 0.0001
Other	0 (0.0)	15 (17.9)	< 0.0001
Ventilatory variables and gas exchange			
Tidal volume, mL/kg of PBW	6.1 (6.0–6.9)	6.6 (6.0–7.0)	0.067
Positive end-expiratory pressure, cm H_2O	10.0 (10.0–12.0)	10.0 (8.0–12.0)	0.0001
Plateau pressure, cm H_2O	21.0 (19.0–22.0)	20 (18.0–22.0)	0.023
Driving pressure, cm H_2O	10.0 (8.0–11.0)	10.0 (9.0–12.0)	0.233
Compliance, mL/cm H_2O	43.0 (35.0–52.0)	41.0 (32.0–50.0)	0.213
Normalized elastance, cm H_2O/(mL/kg PBW)	1.50 (1.30–1.70)	1.46 (1.29–1.73)	0.811
Pa_{O_2}/F_{IO_2}, mm Hg	189 (160–242)	182 (161–213)	0.114
Ventilatory ratio	1.88 (1.54–2.17)	1.71 (1.42–2.20)	0.120
Acute respiratory distress syndrome criteria, *n* (%)	180 (95.0)	66 (77.0)	< 0.001
Mild	75 (41.6)	22 (33.3)	0.240
Moderate	98 (54.4)	36 (54.5)	0.252
Severe	8 (4.4)	7 (10.6)	0.248
Neuromuscular blockers, *n* (%)	125 (66.1)	33 (38.8)	≤ 0.0001
Prone position, *n* (%)	68 (36.0)	11 (13.0)	≤ 0.0001
Sedatives use 24 hr before spontaneous awakening trials			
Richmond Agitation-Sedation Scale, points	−4 (−5 to −4)	−4 (−5 to −4)	0.863
Propofol, *n* (%)	144 (76.0)	65 (73.0)	≥ 0.999
Average dose, mg/kg/hr	2.5 (1.6 to 3.2)	2.0 (1.3 to 2.9)	0.033
Midazolam, *n* (%)	50 (26.0)	14 (16.0)	0.089
Average dose, mg/kg/hr	0.23 (0.15 to 0.35)	0.24 (0.20 to 0.34)	0.451
Fentanyl, *n* (%)	189 (100)	85 (100)	≥ 0.999
Average dose, µg/kg/hr	2.60 (1.90 to 3.10)	2.80 (1.87 to 3.85)	0.241

BMI = body mass index, PBW = predicted body weight.
Variables expressed in mean (SD) or median (interquartile range) according to symmetric or asymmetric distribution, respectively.

Awakening Trials and First PSV Transition

In total, 220 (80.0%) patients assumed PSV on the same day that SAT occurred, whereas 44 (16.0%) did it the following day. None of the patients required an increase in sedation/analgesics during the timeframe between the SAT and PSV switch. The total duration of MV before the first PSV transition was 3.0 days (2.0–6.0). When assuming PSV, the RASS score was −2 (−3 to 0).

According to our definition, 120 of 274 patients (43.7%) failed the first transition to PSV and had to return to controlled MV. When comparing groups, the failure rate was significantly higher in COVID-19 (49.7%) versus non-COVID-19 (30.5%) patients (p = 0.003). The time until failure (**Fig. 2*A***), as well as the specific reasons for failure (**Fig. 2*B***), were similar between groups. In 85/120 (70.8%) of these patients, a continuous infusion of NMBAs was required within 48 hours after failure; in all these cases (85/85), the main reason for blocking was severe hypoxemia ($Pao_2/Fio_2 \leq 150$ mm Hg) not corrected by a new period of controlled ventilation; 31 of 85 subjects had concomitant potentially harmful patient-ventilator asynchronies. In 52 of 85 cases (61.2%), prone position was used because severe hypoxemia persisted after NMBA infusion.

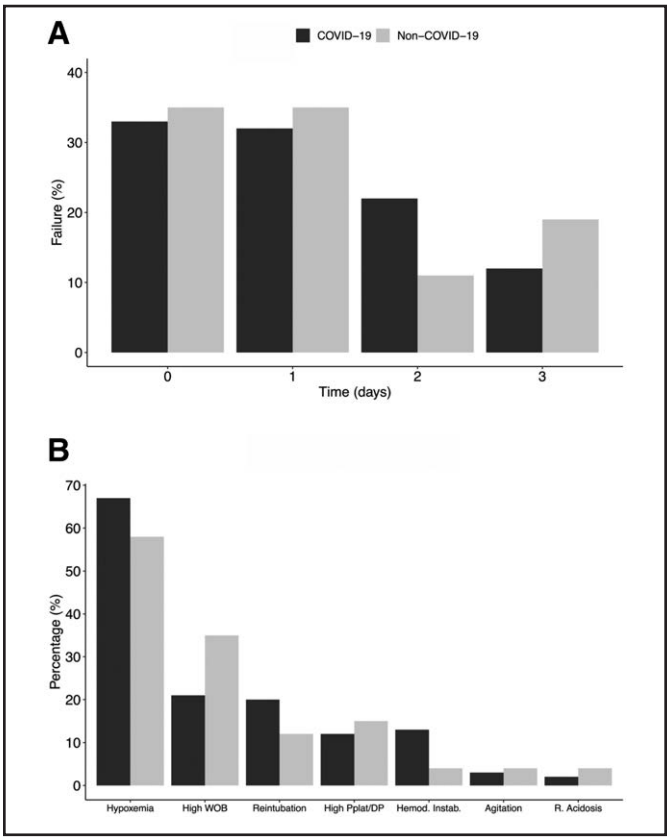

Figure 2. Description of the failure of first transition to pressure support ventilation after awakening trials. **A**, Events of failure according to the calendar day that it occurred. **B**, Main reasons for failure. DP = driving pressure, Pplat = plateau pressure, R. acidosis = respiratory acidosis, WOB = work of breathing.

Risk Factors for Failure

The variables that remained in the final model for predicting the first PSV transition failure are depicted in **Table 2**. After multiple adjustments, COVID-19 diagnosis, receiving NMBAs, and higher fentanyl dose independently increased the chances for failure. Conversely, higher BMI, Pao_2/Fio_2, and pH were protective. The age, nonrespiratory SOFA, and normalized elastance did not modify the failure chances.

Clinical Outcomes

Table 3 shows the results of secondary endpoints. In addition, the cumulative incidence of 60-day definitive MV discontinuation in COVID-19 and non-COVID-19 is shown in **Figure 3**. Overall, the results were significantly worse in failure groups, except for ICU mortality, which was not different in non-COVID-19.

DISCUSSION

This study describes in detail the rate of failure of the first PSV transition after protocolized SAT, its predictors, and associated outcomes in a large cohort of AHRF. Our key findings are as follows: 1) a high proportion of subjects experienced significant deterioration during the first PSV attempt and had to return to controlled ventilation mainly due to severe hypoxemia, 2) this occurred more frequently in COVID-19, 3) COVID-19 diagnosis, NMBAs requirement, higher fentanyl dose, lower Pao_2/Fio_2 and pH before SAT increased the failure chances, whereas higher BMI reduced it, and 4) failure was associated with worse outcomes.

Awakening Trials and First PSV Attempt

To carry out early SATs is mandatory to avoid the negative effects of deep sedation (5, 20, 30, 32). Nevertheless, reducing sedatives rapidly leads to the

TABLE 2.
Multiple Logistic-Regression Model for Failure of First Pressure Support Ventilation Attempt (*n* = 274)

Predictors			
	OR	CI 95%	*p*
COVID-19 diagnosis (yes)	2.22	1.15–4.43	0.020
Fentanyl dose (per 1-µg/kg/hr increase)	1.29	1.05–1.60	0.018
Previous neuromuscular blockers (yes)	2.16	1.15–4.11	0.017
pH (per 0.10-units increase)	0.61	0.38–0.96	0.035
Pao_2/Fio_2 (per 25-mm Hg increase)	0.87	0.78–0.97	0.017
BMI (per 1-kg/m^2 increase)	0.95	0.91–0.99	0.029
Nonrespiratory Sequential Organ Failure Assessment (per 1-point increase)	0.89	0.79–1.00	0.060
Normalized elastance (per 1-cm H_2O/[mL/kg])	1.74	0.91–3.50	0.103
Age (per 1-yr increase)	1.02	1.00–1.04	0.097

BMI = body mass index, OR = odds ratio.

TABLE 3.
Outcomes According to the Results of the First Pressure Support Ventilation Attempt After Awakening Trials

Outcomes	COVID-19 (*n* = 189)			Non-COVID-19 (*n* = 85)		
	Success (*n* = 95)	Failure (*n* = 94)	*p*	Success (*n* = 59)	Failure (*n* = 26)	*p*
Extubation, *n* (%)	72 (76.0)	39 (41.5)	< 0.0001	51 (86.0)	12 (46.0)	< 0.001
Tracheostomy, *n* (%)	20 (21.0)	38 (40.4)	0.005	8 (13.5)	12 (46.0)	0.038
60-d ventilator-free days, d	52.0 (39.0–56.0)	20.5 (0.0–42.0)	<0.0001	52.0 (31.5–55.0)	14.0 (0.0–40.5)	< 0.001
Mechanical ventilation duration, d	8 (4.0–16.5)	18 (11.0–25.7)	<0.0001	7.0 (4.0–10.5)	18 (9.5–27.8)	< 0.0001
ICU length of stay, d	11.0 (6.0–20.0)	18.0 (11.0–26.0)	0.001	13.0 (10.0–19.0)	27.0 (16.0–36.0)	0.001
ICU mortality, *n* (%)	9 (10.0)	40 (42.5)	<0.001	14 (23.7)	11 (42.0)	0.083

Variables expressed in mean (SD) or median (interquartile range) according to symmetric or asymmetric distribution, respectively.

challenge of transitioning to assisted ventilation, which may be poorly tolerated in patients with injured lungs (8, 10, 12, 33). In this setting, the failure of the first transition from controlled to assisted ventilation has not been precisely defined. Esnault et al (12) observed respiratory deterioration in 9 of 28 patients (32.0%) with COVID-19 within 24 hours of assuming PSV. The higher failure rate of our COVID-19 cohort could be explained by the different temporal criteria considered in our definition. Accordingly, if we only consider the first 24 hours of PSV, the failure rate was 33.8%. In addition, the failure rate of our non-COVID-19 cohort (30.5%) may be comparable with previous studies. Van Haren et al (8) reported that 22.0% of ARDS patients returned to controlled MV within 24 hours of assuming PSV. In a randomized trial, Mauri et al (10) observed assisted ventilation failure in 23.0% of the experimental group and in 30.0% of the control group. In the above study, a large proportion of events were explained by severe hypoxemia, which coincides with our findings. Overall, these data suggest that nearly one-third of patients recovering from AHRF will not

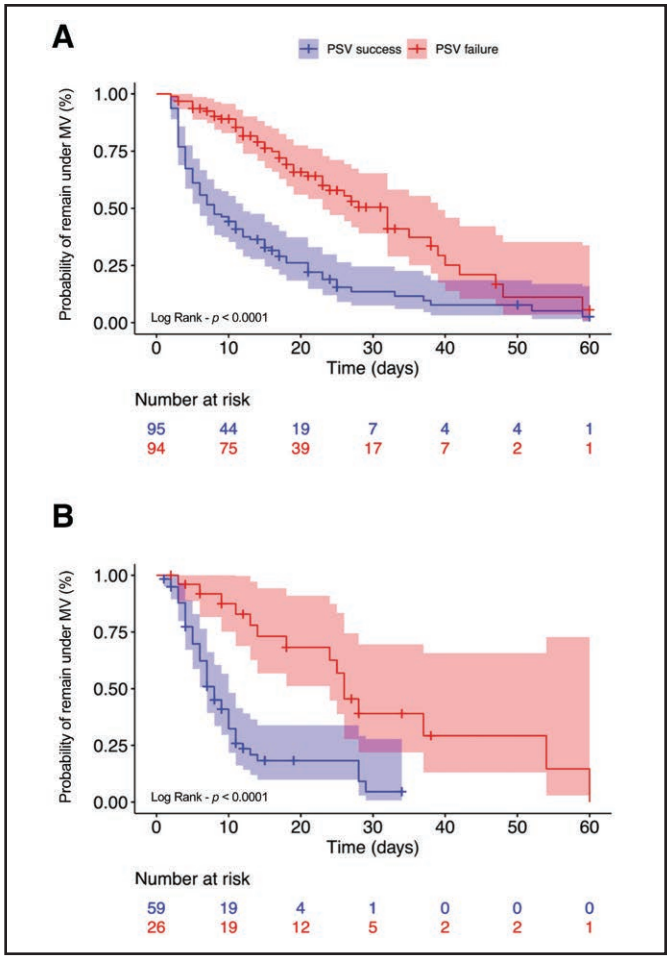

Figure 3. Proportion of patients with COVID-19 (**A**) and non-COVID-19 (**B**) respiratory failure under invasive ventilation at day 60. MV = mechanical ventilation, PSV = pressure support ventilation.

tolerate assisted ventilation when sedation is reduced, and this phenomenon may occur more frequently in COVID-19.

Risk Factors for Failure

Although the patients met SAT safety criteria, our failure rate was higher than that reported in the study by Girard et al (20) (7.0%) using a similar coupled SAT plus SBT approach. However, both studies differ in some aspects: First, less hypoxemic patients were included (≈50%) in Girard's study; second, their starting point to measure SAT outcomes (failure or success) was "sedation interruption," whereas, independently of when sedatives were suspended, it was "PSV initiation" in our study; third, they considered SAT success if patients "opened their eyes" or "tolerated sedative interruption for 4 hours," without considering if PSV transition occurred or not (of note, 82.0% of successful events were explained by the first criteria). Consequently, it is unknown if patients were already under PSV at the time of failure in the above study. In the same way, we cannot precisely determine when the patients opened their eyes, or how many failure events occurred before 4 hours of SAT owing to data collection limitations. Finally, it is worth noting that, "SBT" and "PSV-transition" are different stages in the process of gradually liberating patients from ventilatory support. In this sense, depending on subject's condition and/or type of sedatives used, some patients can be under PSV for several days until reaching the SBT "milestone," only a few minutes or, simply never perform one (1, 21, 22).

In our logistic-regression model, a positive COVID-19 diagnosis increased failure odds by more than two-fold. These patients have been shown to present high respiratory drive and effort, leading to poor PSV tolerance (12); in this context, the uncontrolled/impaired immune response impeding the acceptable recovery of the underlying lung injury seems the most likely explanation (34). However, the recovery time under controlled MV before PSV transition did not affect failure chances, highlighting that the natural evolution of the disease may be heterogeneous. Additionally, receiving NMBAs and increasing fentanyl dose together with higher hypoxemia and acidosis preceding SAT was associated with a higher probability of failure. We believe that these predictors may be interpreted as different markers of increased illness severity of patients who failed. Furthermore, the fentanyl dose could be a potentially modifiable factor. Opioids are known to alter respiratory patterns resulting in high V_T which may further difficult protective ventilation (35, 36). Likewise, acidosis and hypoxemia might stimulate inspiratory effort and jeopardize assisted ventilation when the central drive depressants are suspended (37). Surprisingly, higher BMI prevented failure. Previous studies have shown that high PEEP may be more helpful in relieving the work of breathing and improving gas exchange in obese than in nonobese individuals (38–40), which might partially explain this protective association.

Clinical Outcomes

The association between the failure of the first PSV transition and outcomes should be considered with caution. Our predictive model indicates that failure was

more probable in sicker patients. With this in mind, the potential causal link between failure and clinical events deserves further confirmation, and the inability to sustain PSV might be considered as an additional marker of severity. However, assisted ventilation led to profound hypoxemia in most of the patients who failed, which albeit hypothetical in nature, could have modified the patient's clinical course. Bachmann et al observed persistent severe hypoxemia in ARDS models undergoing PSV even after 4 hours of a recovery period under protective MV (41). Similarly, we observed wide NMBAs and prone requirements after failure due to severe hypoxemia, which unfaithfully delayed ventilator weaning and prolonged MV. Accordingly, the definite discontinuation of MV was lower in failure groups, suggesting that the intolerance to spontaneous modes might be an additional factor hindering patient's weaning (30, 42). Finally, longer MV duration and its associated complications might increase mortality. Similarly, Van Haren et al (8) reported higher mortality in ARDS patients who returned to controlled ventilation within 24 hours of PSV.

Clinical Implications

Even though causality cannot be ensured and our results only support associations, the potential relationship between failure and worse outcomes suggests that the decision of giving full control of ventilation to patients with a still-recovering lung disease should be carefully analyzed. Our predictors provide information to identify when the failure chances may be higher. In the future, it may be interesting to test whether allowing spontaneous breathing too early could destabilize the patient and potentially lengthen the weaning duration. Currently, daily sedative interruption is strongly prioritized (6, 20, 23); subsequently, a case-by-case evaluation is warranted to determine whether switching to full spontaneous modes is safe. Afterward, clinicians should be aware that some patients, especially the more severe ones, may require close monitoring during PSV, where simple bedside indexes like P0.1 and airway occlusion pressure may help to detect an early worsening (12).

Limitations

Our study has several limitations. The retrospective nature of the data and single-center design suggest that our results should be considered hypothesis-generating. The characteristics of patients at ICU admission and the changes in healthcare imposed by the pandemic may have influenced the results and limited their generalizability to nonpandemic situations (43, 44). The prohibition of using noninvasive ventilation in COVID-19 may have affected outcomes and comparisons with non-COVID-19. Widely accepted criteria for defining assisted ventilation failure are difficult to establish; additionally, the decision to declare failure could have varied among clinicians and epochs over a more than 4-year period. To improve external validity, we collected reasons for failure in detail and grouped them based on similar previous definitions (8, 10, 12). Furthermore, assigning to spontaneous assisted ventilation the complete responsibility for all the complications that triggered the decision to return to controlled MV may be debatable. However, none of the patients exhibited failure criteria in the timeframe between SAT and PSV transition, suggesting that spontaneous breathing might be a major destabilizing factor. We did not assess whether using alternative spontaneous modes (e.g., proportional-assisted ventilation) could have reduced the failure or improved the outcomes. These promising modalities may better optimize lung protection and diaphragm protection, whose benefits are awaiting confirmation (NCT02447692) (45). Lastly, considering the large number of secondary endpoints, these findings should be interpreted as exploratory.

CONCLUSIONS

After systematic awakening trials, the failure of the first PSV transition is present in a great proportion of AHRF patients and is higher in COVID-19 pneumonia. Positive COVID-19 diagnosis, previous neuromuscular blockers, higher fentanyl dose, acidosis, and hypoxemia are risk factors for failure, while a higher BMI is protective. The failure is associated with poor outcomes.

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