Statistical Analysis Report

Title	Assessing Ventilator Safety in Patients on Pressure-support Ventilation (ASOP)
CRU/Department/Division/Center	Pulmonary, Allergy, and Critical Care Medicine
IRB Number	Pro00106860
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1 Statistical Analysis Plan

1.1 Study Overview

Background/Introduction:

Ventilator-induced lung injury (VILI) is a known cause of significant morbidity and mortality in patients with acute respiratory failure. Lung injury caused by large tidal volumes, high pressures, repetitive airway collapse, and large changes in trans-pulmonary pressure during a breath are all known to cause VILI. It has also been noted that similar lung damage can be cause by large, patient generated, uncontrolled tidal volumes and driving pressures – termed 'self-induced lung injury' (SILI). Patient-generated large tidal volumes may be disease induced (e.g. neurologic injury) or driven by other factors (metabolic derangements, anxiety). Interactions of patient efforts with assisted/supported models of mechanical ventilation may worsen this.

Pressure-support ventilation (PSV) is a common mechanical ventilation mode, often used in patients with active inspiratory efforts in order to reduce patient inspiratory work and improve comfort. PSV effectively allows spontaneously breathing patients to determine their breath flow-rate and breath duration, eliminating flow and cycle dyssynchrony.

1.1.1 Study Aims

1. Determine the internal consistency of four methods of measuring airway plateau pressure during pressure-support ventilation, utilizing:
    a. The static respiratory driving pressure from ventilator in pressure support during inspiratory hold (Maneuver A; considered the gold-standard measurement)
    b. The lung driving pressure in pressure support during first 0.1 seconds of inhalation (Maneuver B)
    c. The occlusion pressure in pressure support (Maneuver C)
    d. The static respiratory system driving pressure in volume control (Maneuver D)
2. The pairwise consistency of measures (AB, AC, AD, BC, BD, CD)

1.2 Study Population

1.2.1 Inclusion Criteria

- Adult patients with acute respiratory failure receiving invasive mechanical ventilation at Duke University Medical Center, managed in pressure-support mode of ventilation

1.2.2 Exclusion Criteria

- Actively undergoing a spontaneously awakening trial (SAT)
- Patient or surrogate unable to provide informed consent
- Currently pregnant
- Currently incarcerated
- Acute exacerbation of an obstructive lung disease
- Known esophageal varices or any other condition for which the attending physician deems an orogastric catheter to be unsafe
- Esophageal, gastric, or duodenal surgical procedure(s) within the last 6 months

1.2.3 Data Acquisition

Study design	Prospective cohort study
Data source/how the data were collected	Data entered directly into REDCap by study staff
Contact information for team member responsible for data collection/acquisition	Elias Pratt
Date or version (if downloaded, provide date)	February 22, 2024
Data transfer method and date	Downloaded directly from REDCap
Where dataset is stored	BiostatsCore\CRU\Pulmonary\Elias Pratt\Pro00106860 ASOP\Data\

1.3 Outcomes, Exposures, and Additional Variables of Interest

1.3.1 Maneuver Variables

Maneuver	**Variable(s)**	**Description**	**Specifications**

A	dprs_servo[1-5]	Static Respiratory System Driving Pressure from Ventilator	Calculated within REDCap as: pplat_servo_a[1-5] – peep_vent_a_[1-5]
B	p0_1_[1-5]	P 0.1 from Servo	Entered directly into REDCap
C	paw_max_b[1-5]	Max Airway Pressure	Entered directly into REDCap
	peep_vent_b[1-5]	PEEP from Ventilator	Entered directly into REDCap
	aop_[1-5]	Airway Occlusion Pressure	Calculated within REDCap as: peep_vent_c[1-5] – max_neg_paw[1-5]
	pred_delta_pl_[1-5]	Predicted ΔP_L	Calculated as: paw_max_b[1-5] – peep_vent_b[1-5] + (2/3)*aop_[1-5]
D	dprs_stat_vc_d[1-5]	Static Respiratory System Driving Pressure	Calculated within REDCap as: pplat_aw_d[1-5] – peep_vent_d[1-5]

1.3.2 Demographic and Clinical Characteristics

Variable	**Description**	**Variables and Source**	**Specifications**
Sex	Patient sex	sex	1. Male 2. Female
Ethnicity	Patient ethnicity	ethnicity	1. Not Hispanic or Latino 2. Hispanic or Latino 3. Unknown or Not Reported
Race	Patient race	race	1. White 2. Black 3. Asian 4. Native American or Alaska Native 5. Native Hawaiian or Pacific Islander 6. More than one race 7. Unknown or Not Reported
Age at intubation	Patient age at intubation	Derived from dob and date_study	
Days of ventilation	Days of mechanical ventilation	mv_days	

Height	Patient height (cm)	height	
Weight	Patient weight (kg)	weight	
BMI	Patient BMI	bmi	
Ideal body weight	Patient ideal body weight	ibw	• Male: 50 + .91 * height – 152.4 • Female: 45 + .81 * height – 152.4
cc/Kg	6 cc/kg of ideal body weight	cc_kg	6 * ibw
Admission diagnosis	Admission diagnosis/cause of respiratory failure	admit_diag, other_cause_admisison	1. ARDS 2. Post-surgical 3. Trauma 4. Heart-Failure 5. Cardiac Arrest 6. Stroke 7. Other
APACHE II Score	Total APACHE II score	ap2_total_score	
APACHE II Classification	Interpretation of APACHE II score	ap2_interpretation	1. 0-4: 4% death rate 2. 5-9: 8% death rate 3. 10-14: 15% death rate 4. 15-19: 25% death rate 5. 20-24: 40% death rate 6. 25-29: 55% death rate 7. 30-34: 75% death rate 8. >34: 85% death rate

1.4 Statistical Analysis Plan

1.4.1 Demographic and Clinical Characteristics (“Table 1”)

The variables listed in Section 3.2 will be summarized for the cohort using mean with standard deviation, median with 25th and 75th percentiles (Q1, Q3), and min-max for continuous measures, and frequency with percentage for categorical measures.

1.4.2 Analyses Plan for Aim 1

The internal consistency of the static respiratory driving pressure (DPRS), that is to say the consistency of DPRS measures from the same patient, will be quantified for each maneuver (A, B, C, and D) separately using the intraclass correlation coefficient (ICC). The ICC measures the correlation of two observations coming from the same patient.

Specifically, the ICC is defined as

$$ICC = \frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \sigma_\epsilon^2}$$

Where σ_α^2 is the variation in DPRS measurements between different patients, and σ_ϵ^2 gives the within-patient variation of DPRS measurements, with the sum $\sigma_\alpha^2 + \sigma_\epsilon^2$ giving the total variation in DPRS values across all patients. Therefore, the ICC measures the proportion of total variation in the DPRS measurements that is due to variation between patients.

95% confidence intervals for each of the within-patient and between-patient variances, as well as the ICC, will be calculated using the empirical 2.5th and 97.5th percentiles of 10,000 parametric bootstrap replications.

General guidelines for interpretation of ICC values are as follows (Cicchetti, 1994):

- <0.40: poor consistency
- 0.40-0.59: fair consistency
- 0.60-0.74: good consistency
- 0.75-1.00: excellent consistency

Technical details:

The values of σ_α^2 and σ_ϵ^2 will be estimated from a linear mixed-effects model, with

$$Y_{ij} = \mu + \alpha_i + \epsilon_{ij}$$

With Y_{ij} being the jth DPRS measurement from the ith patient, with up to 5 measurement each from the 15 patients enrolled.

Here, the underlying mean DPRS value is μ and the subject-specific deviation from the overall mean is given by α_i for the ith patient, and the within-patient variation of measurements is given by ϵ_{ij}.

We assume that

$$\alpha_i \sim N(0, \sigma_\alpha^2), \epsilon_{ij} \sim N(0, \sigma_\epsilon^2)$$

With α_i and ϵ_{ij} each iid and independent of each other.

1.4.3 Analyses Plan for Aim 2

For each pair of maneuvers, the consistency of the measures between the two methods will be quantified using the interclass correlation coefficient ρ_{inter}.

ρ_{inter} gives the correlation between any two measurements from the same patients from different methods.

Similarly to Aim 1, the ρ_{inter} is defined as

$$\rho_{inter} = \frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2}$$

95% confidence intervals for each of the variances, as well as the ICC, will be calculated using the empirical 2.5th and 97.5th percentiles of 10,000 parametric bootstrap replications.

For each maneuver, the within-subject mean values will be calculated. For each pair of maneuvers (A and B, A and C, etc) the subject-level mean values will be plotted.

Summaries of the subject-level mean and standard deviations will be reported using mean with standard deviation, median with first and third quartiles, and range, stratified by maneuver.

Technical details:

The values for $\sigma_\alpha^2, \sigma_\gamma^2, \sigma_\epsilon^2$ are estimated from the linear mixed effects-model

$$Y_{ijk} = \mu + \alpha_i + \beta_j + \gamma_{ij} + \epsilon_{ijk}$$

Where Y_{ijk} is the kth measurement coming from the ith patient using method j.

Here, i indexes the 15 patients, j indexes the either the first or second of the two methods (A or B, A or C, etc), and k indexes the breath number for patient i on method j. Because some measurements were discarded, each patient on each method has up to, but sometimes less than, 5 repetitions.

The various terms represent:

- $\mu =$ the overall mean value for method 1
- $\alpha_i =$ the subject-specific deviation from the overall mean for method 1
- $\mu + \alpha_i$ = the subject-specific mean for method 1
- $\beta_j =$ the deviation in the overall mean for method 2 from method 1
- $\mu + \beta_j =$ the overall mean for method 2
- $\gamma_{ij} =$ the subject-specific interaction term for method 2 (relative to the subject-specific deviation for method 1)
- $\alpha_i + \gamma_{ij}$ = the subject-specific deviation from the overall mean for method 2

We assume that

$$\alpha_i \sim N(0, \sigma_\alpha^2), \qquad \gamma_{ij} \sim N(0, \sigma_\alpha^2), \qquad \epsilon_{ijk} \sim N(0, \sigma_\epsilon^2)$$

With α_i, γ_{ij}, and ϵ_{ijk} each iid and mutually independent of each other.

1.4.4 Bland-Altman Plot

A Bland-Altman (Tukey mean-difference) plot will be created for maneuvers A and D.

This plot will show the difference between measurements on the y-axis, and the average of measurements on the x-axis. 95% limits of agreement are calculated for the difference between measurements (y-axis) values by calculating the usual 95% confidence interval for the mean of the differences (that is, roughly, [mean of differences] ± 1.96 * [standard deviation of the differences]).