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Authors

Lanspa, Michael J
Gong, Michelle Ng
Schoenfeld, David A
et al.

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Prospective Assessment of the Feasibility of a Trial of Low–Tidal Volume Ventilation for Patients with Acute Respiratory Failure

Michael J. Lanspa[1,2], Michelle Ng Gong[3], David A. Schoenfeld[4,5], Kathleen Tiffany Lee[4,5], Colin K. Grissom[1,2], Peter C. Hou[6], Ary Serpa-Neto[7], Samuel M. Brown[1,2*], Theodore J. Iwashyna[8], Donald M. Yealy[9], Catherine L. Hough[10], Roy G. Brower[11], Carolyn S. Calfee[12], Robert C. Hyzy[8], Michael A. Matthay[12], Russell R. Miller III[1,2], Jay S. Steingrub[13], B. Taylor Thompson[4], Chadwick D. Miller[14], Terry P. Clemmer[2,15], Gregory W. Hendey[16], David T. Huang[9], Kusum S. Mathews[17], Nida Qadir[16], and Mark Tidswell[18], and the National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung injury (PETAL) Clinical Trials Network

[1]Intermountain Medical Center and [2]University of Utah, Salt Lake City, Utah; [3]Montefiore Healthcare Center, Albert Einstein College of Medicine, Bronx, New York; [4]Massachusetts General Hospital, Harvard University, Boston, Massachusetts; [5]Harvard T. H. Chan School of Public Health, Boston, Massachusetts; [6]Brigham and Women's Hospital, Harvard University, Boston, Massachusetts; [7]Hospital Israelita Albert Einstein, São Paulo, Brazil; [8]University of Michigan, Ann Arbor, Michigan; [9]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [10]University of Washington, Seattle, Washington; [11]Johns Hopkins University School of Medicine, Baltimore, Maryland; [12]University of California, San Francisco, San Francisco, California; [13]University of Massachusetts Medical School–Baystate, Springfield, Massachusetts; [14]Wake Forest Baptist Health, Winston Salem, North Carolina; [15]LDS Hospital, Salt Lake City, Utah; [16]University of California, Los Angeles, Los Angeles, California; [17]Icahn School of Medicine at Mount Sinai, New York, New York; and [18]Baystate Medical Center, Springfield, Massachusetts

ORCID ID: 0000-0002-8810-2794 (K.S.M.).

Abstract

Rationale: Low–tidal volume ventilation (LTVV; 6 ml/kg) benefits patients with acute respiratory distress syndrome and may aid those with other causes of respiratory failure. Current early ventilation practices are poorly defined.

Objectives: We observed patients with acute respiratory failure to assess the feasibility of a pragmatic trial of LTVV and to guide experimental design.

Methods: We prospectively enrolled consecutive patients with acute respiratory failure admitted to intensive care units expected to participate in the proposed trial. We collected clinical data as well as information on initial and daily ventilator settings and inpatient mortality. We estimated the benefit of LTVV using predictive linear and nonlinear models. We simulated models to estimate power and feasibility of a cluster-randomized trial of LTVV versus usual care in acute respiratory failure.

Results: We included 2,484 newly mechanically ventilated patients (31% with acute respiratory distress syndrome) from 49 hospitals. Hospital mortality was 28%. Mean initial tidal volume was 7.1 ml/kg predicted body weight (95% confidence interval, 7.1–7.2), with 78% of patients receiving tidal volumes less than or equal to 8 ml/kg. Our models estimated a mortality benefit of 0–2% from LTVV compared with usual care. Simulation of a stepped-wedged cluster-randomized trial suggested that enrollment of 106,361 patients would be necessary to achieve greater than 90% power.

Conclusions: Use of initial tidal volumes less than 8 ml/kg predicted body weight was common at hospitals participating in the National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury (PETAL) Network. After considering the size and budgetary requirement for a cluster-randomized trial of LTVV versus usual care in acute respiratory failure, the PETAL Network deemed the proposed trial infeasible. A rapid observational study and simulations to model anticipated power may help better design trials.

Keywords: mechanical ventilation; lung-protective ventilation; low-stretch ventilation; low–tidal volume ventilation; acute respiratory distress syndrome

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Authors Contributions: M.N.G., C.K.G., and P.C.H.: conceived of this study; D.A.S. and K.T.L.: analyzed data and performed statistical analyses; and M.N.G. and M.J.L.: drafted the manuscript. All authors on the writing committee contributed to the study design and patient enrollment. All authors revised the manuscript for important intellectual content, and all authors reviewed and approved the manuscript in its final form.

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In 2000, the National Heart, Lung, and Blood Institute (NHLBI) Acute Respiratory Distress Syndrome Network (ARDSNet) demonstrated improved survival among patients with acute respiratory distress syndrome (ARDS) receiving tidal volume (V_T) targeted to 6 ml/kg of predicted body weight (PBW) compared with a V_T targeted to 12 ml/kg PBW (1). As a result, low–tidal volume ventilation (LTVV) is now recommended for all patients with ARDS, although penetration of this evidence-based practice has been limited, especially early in mechanical ventilation (2–8). LTVV may also benefit patients without ARDS (9–12). Consequently, there has been increasing call to apply LTVV for all patients with acute respiratory failure upon initiation of mechanical ventilation (13–15).

The Prevention and Early Treatment of Acute Lung Injury (PETAL) Network is a multicenter clinical trials network funded by the NHLBI to conduct clinical trials to prevent and treat ARDS. The PETAL Network considered performing a pragmatic stepped-wedge, cluster-randomized, controlled, hybrid implementation trial, entitled Low Tidal Volume Universal Support (LOTUS), to examine systematic implementation of a default 6 ml/kg PBW LTVV strategy in patients with acute respiratory failure requiring intubation to improve adherence to LTVV and decrease mortality in acute respiratory failure. Typically, trial design is based on estimates of event rate, effect size, and sample size applied to analytical formulas. However, in a stepped-wedged cluster design, it is necessary to also account for additional factors such as the size of clusters, variation in event rates within the clusters, and correlations among patients within a given cluster. Especially important for LOTUS was the current usual-care practice at PETAL sites and the realistic absolute effect size derived from lowering usual-care V_T to 6 ml/kg PBW. Trial planning, especially in specific designs such as we considered, may be better estimated by simulation than routine, simplistic calculations, but such simulations require detailed data of initial parameters (16).

The PETAL Network collected data from network sites to aid in the development of a simulation model to determine the power and feasibility for recruitment for the LOTUS trial (LOTUS-FRUIT). LOTUS-FRUIT had two main goals: *1*) to conduct a prospective, observational study within all PETAL Network sites to determine the frequency of and outcomes from acute respiratory failure and the current usual care for V_T ventilation in patients with and without ARDS; and *2*) to simulate the design and power of the proposed LOTUS trial.

Methods

Cohort Study

We conducted a multicenter, prospective, observational cohort study of patients with acute respiratory failure on mechanical ventilation in the PETAL Network hospitals. We enrolled consecutive patients up to 100 patients per hospital within a 30-day period between July 1 and October 1, 2016. We included patients (aged ⩾18 yr) who presented with acute respiratory failure, defined solely as those requiring invasive mechanical ventilation via an endotracheal tube who received care in the intensive care unit (ICU). We excluded patients receiving chronic invasive mechanical ventilation through a tracheostomy, admitted to an ICU after elective surgery, presenting to the study hospital after more than 24 hours of invasive mechanical ventilation, or extubated before transfer to the ICU. We also excluded patients admitted to ICUs deemed unlikely to participate in a future trial of initial LTVV.

For all patients, we collected baseline demographic data, the hospital location (emergency department, ward, ICU, operating room), indication for intubation (hypoxemic or hypercapnic respiratory failure or both, altered level of consciousness, or surgery), type of ICU, and Sequential Organ Failure Assessment (17) score in the first 24 hours after intubation. For all patients, we collected baseline ventilator data immediately after intubation, arterial blood gas results and oxygen saturation as measured by pulse oximetry, and presence of ARDS. ARDS was defined as a ratio of arterial oxygen tension to fraction of inspired oxygen ($F_{I_{O_2}}$) less than or equal to 300 (corrected for altitude at two centers by multiplying 300 × ambient barometric pressure divided by sea-level barometric pressure) with a chest radiograph (reviewed by a site investigator) within 24 hours of the qualifying ratio of arterial oxygen tension to $F_{I_{O_2}}$ that had bilateral infiltrates unexplained by mass, collapse, or effusion (18). For the first 50 patients enrolled at each hospital, we also collected daily data on ventilator mode, V_T, and presence of ARDS for the first 3 days (as opposed to only the first day) after intubation. We calculated V_T indexed to PBW from the set V_T for patients on ventilator mode with volume settings (volume controlled, pressure-regulated volume control, volume-synchronized intermittent mandatory ventilation). For patients on pressure ventilation modes (pressure controlled, pressure support, pressure-synchronized intermittent mandatory ventilation, pressure inverse ratio ventilation), we calculated V_T from the ratio of minute ventilation (in ml/min) to the respiratory rate. We followed enrolled patients until hospital discharge or 28 days (whichever came first) for clinical outcomes including mortality, ventilator-free days (VFD) to Day 28, and length of stay. The PETAL Network central institutional review board at Vanderbilt University (160825) approved the study design, including a waiver of the requirement for informed consent.

Statistical Analysis

We report central tendencies using mean and standard deviation or standard error, median, and interquartile range (IQR) as appropriate. We compared summary statistics using Fisher's exact test, analysis of variance, and Wilcoxon rank-sum test when appropriate.

Simulation Model Development

Estimation of effect size from reduction of V_T to 6 ml/kg PBW. To determine the possible improvement in mortality that could be observed with a reduction in V_T from current usual care in the LOTUS-FRUIT cohort to 6 ml/kg PBW, we estimated mortality as a function of initial V_T. We used

Correspondence and requests for reprints should be addressed to Michelle Ng Gong, M.D., Division of Critical Care Medicine, Montefiore Medical Center, 111 East 210th Street, Main Floor, Gold Zone, Bronx, NY 10026. E-mail: mgong@montefiore.org.

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five models based on data from three distinct patient populations. First, we built mortality models using data from the Practice of Ventilation in Critically Ill Patients Without ARDS (PRoVENT) study (19), an observational cohort of patients with acute respiratory failure without ARDS. We developed two logistic regression models predicting mortality: one assuming a linear relationship between VT and mortality, the other a spline model with knots at 6, 8, 10, and 12 ml/kg PBW. PRoVENT Day 2 VT was used in the simulation because baseline VT was not associated with mortality (19). Second, we created a logistic regression model using the ARDSNet VT trial data for VT on Day 1 of the trial, mortality, and VFD (1). We also created a multivariate model predicting mortality assuming a linear relationship between initial VT and mortality from the LOTUS-FRUIT cohort (*see* online supplement). In that model only, we controlled for possible confounding and developed propensity scores for baseline VT using inverse probability of treatment weighting using the ipwpoint package for R (20). The propensity model we used was a nonlinear regression model of the probability of receiving a specified VT as a function of the relevant covariates. *See* the online supplement for results of the inverse probability weighting of mortality by baseline VT.

We used the PRoVENT linear model and spline models, as well as the ARDSNet linear model to estimate the potential clinical benefit of switching patients from usual care to LTVV. None of the other linear models showed a benefit for LTVV, and a Loess smooth curve was too variable to use for a fitted model. For each model, the predicted mortality on the patients' current VT (truncated to be between 6 and 12 ml/kg PBW) was subtracted from their mortality on LTVV.

Development of simulation model for LOTUS trial. We first assumed that the LOTUS trial would occur over a maximum of 4 years, because usual clinical practice would likely change substantially over time for a trial lasting longer than 4 years. We assumed the number of patients with acute respiratory failure per month, the baseline preintervention mortality rate, and mean VT to be identical to those in the LOTUS-FRUIT cohort.

We performed 500 simulations of a stepped-wedge, cluster-randomized clinical trial using the model with greatest predicted benefit for lowering the VT to 6 ml/kg PBW in LOTUS-FRUIT sites. For each simulated trial, we randomized the time that each site would receive the intervention as we would do in an actual stepped-wedge design with these sites. We stratified the analysis into two groups based on site size. We then predicted each patient's mortality during the control period and the intervention period, scaled by the ratio of the site's actual mortality to its predicted mortality. For the former, we used the patient's actual VT (truncated to be between 6 and 12 ml/kg PBW), and for the latter, we used 6 ml/kg PBW. With these parameters, we then simulated the mortality rate of each site by month and fit a model which assumed that mortality had a logistic distribution which was quadratic in period (to remove secular trends) and depended on treatment. We included a random interaction effect between site and treatment. We also simulated models with variable adherence to the intervention. Last, we tested the effect of excluding sites with high baseline use of LTVV on the study's power.

Results

LOTUS-FRUIT Prospective Cohort

Acute respiratory failure: frequency, outcomes, and development of ARDS. We enrolled 2,848 patients into the LOTUS-FRUIT cohort from 49 hospitals over a 30-day period between July and September 2017. Enrollment varied by hospital, ranging from 4 to 100 patents, the maximum enrollment allowed per site. Patient characteristics are detailed in Table 1. The predominant reason for intubation was hypoxemic respiratory failure (33.1%), followed by altered mental status (28.3%). Inpatient mortality was 27.8%, and ARDS criteria were met in 31.4% ($n = 895$) of patients. Patients intubated for acute hypoxemic respiratory failure and acute

Table 1. Patient characteristics and outcomes for the total study cohort and stratified by presence of acute respiratory distress syndrome

	Total (*N = 2,848*)	ARDS (*n = 895*)	Non-ARDS (*n = 1,953*)
Age, yr, mean (SD)	56.3 (17.4)	58.3 (16.3)	55.4 (17.9)
Female sex	1,123 (39.4%)	366 (40.9%)	757 (38.8%)
Reason for intubation			
Acute hypoxemia	944 (33.1%)	429 (47.9%)	515 (26.4%)
Altered mental status	805 (28.3%)	146 (16.3%)	659 (33.7%)
Emergent surgery	376 (13.2%)	75 (8.4%)	301 (15.4%)
Acute hypoxemia and hypercapnia	249 (8.7%)	110 (12.3%)	139 (7.1%)
Acute hypercapnia	162 (5.7%)	60 (6.7%)	102 (5.2%)
Metabolic abnormalities	29 (1%)	8 (0.9%)	21 (1.1%)
Other/unclear	283 (9.9%)	67 (7.5%)	216 (11.1%)
Risk factors for ARDS			
Aspiration	329 (13.7%)	149 (16.6%)	180 (9.2%)
Pneumonia	407 (17%)	266 (29.7%)	141 (7.2%)
Sepsis	562 (23.4%)	300 (33.5%)	262 (13.4%)
Shock	367 (15.3%)	190 (21.2%)	177 (9.1%)
Trauma	343 (14.3%)	88 (9.8%)	255 (13.1%)
Location of intubation			
ICU	847 (29.7%)	346 (38.7%)	501 (25.7%)
Emergency department	755 (26.5%)	194 (21.7%)	561 (28.7%)
Operating room	420 (14.7%)	92 (10.3%)	328 (16.8%)
Referring hospital	400 (14%)	113 (12.6%)	287 (14.7%)
Emergency medical services (prehospital)	275 (9.7%)	82 (9.2%)	193 (9.9%)
Hospital ward	151 (5.3%)	68 (7.6%)	83 (4.2%)
SOFA score on Day 1	6 (3–9)	7 (5–10)	4.5 (2.5–7)
ICU length of stay, d	6 (2–11)	7 (4–14)	4 (2–10)
Hospital length of stay, d	11 (5–23)	13 (7–28)	10 (5–20)
Ventilator-free days up to 28 d	23 (0–27)	16 (0–25)	25 (0–27)
Hospital mortality	793 (27.8%)	319 (35.6%)	474 (24.3%)

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ICU = intensive care unit; SD = standard deviation; SOFA = Sequential Organ Failure Assessment.
Age is reported as mean with standard deviation. All other continuous data are reported as median with interquartile range.

Table 2. Simulation of study power for Low Tidal Volume Universal Support Interventional Trial using a stepped-wedge study design

Exclusion of Sites with High Adherence to 6 ml/kg Tidal Volume in Acute Respiratory Failure	Number of Study Sites	Intervention Adherence Rate	Power ± Standard Deviation	Number of Patients in Trial
0 (No exclusion)	49 (all)	1.0	96 ± 3%	107,373
0 (No exclusion)	49 (all)	0.8	96 ± 4%	107,383
Excluding top 10 sites	39	0.8	99 ± 2%	93,739
Excluding top 20 sites	29	0.8	86 ± 2%	66,366

We simulated scenarios based on excluding the sites with the highest baseline adherence to low–tidal volume ventilation, and scenarios based on 100% or 80% adherence to the study intervention.

hypoxemic and hypercapnic respiratory failure had the highest rate of ARDS (*see* Table E1 in the online supplement). We observed the highest mortality rate among patients with metabolic abnormalities and acute hypoxemic respiratory failure (Table E1). Among the 895 patients with ARDS, 684 (76%) met ARDS criteria at the first assessment after initial intubation, another 186 patients (21%) met criteria 1 day after intubation, and the rest met criteria over the next 2 days.

In the first 28 days after initiation, patients were alive and free from mechanical ventilation for a median of 23 days (IQR, 0–27) after intubation. Median duration of ICU stay was 6 days (IQR, 2–11), and median hospital stay was 11 days (IQR, 5–23). Patients with ARDS at intubation, compared with patients without ARDS, spent fewer days free from mechanical ventilation (median, 16; IQR, 0–25; vs. 25; IQR, 0–27; $P < 0.0001$), more days in the ICU (median, 7; IQR, 4–14; vs. 4; IQR, 2–10; $P < 0.0001$), and more days in the hospital (median, 13; IQR, 7–28; vs. 10; IQR, 5–20; $P < 0.0001$) (Table 1). Patients with ARDS had higher observed in-hospital mortality (35.6%) than patients without ARDS (24.3%) ($P < 0.0001$). Additional data on differences in baseline characteristics and outcomes by reason for intubation and ARDS status are provided in Table E1.

Usual practice for VT in acute respiratory failure. Initial VT, indexed to PBW, was available for 2,543 (89%) patients. Use of LTVV was common. Average initial VT in acute respiratory failure was 7.1 ml/kg PBW (95% confidence interval [CI], 7.1–7.2), which is similar to the average VT used in patients with ARDS at 7.2 ml/kg PBW (95% CI, 7.1–7.3) (Figures E2A and E2C). Overall, 21.8% (95% CI, 19.9–23.9%) of patients with acute respiratory failure received VT greater than 8 ml/kg PBW. Similarly, 21.0% (95% CI, 18.7–23.5%) of patients with ARDS received VT greater than 8 ml/kg PBW (Figures E1B and E1D). Some sites have already adopted LTVV with mean VT less than or equal to 6.5 ml/kg in acute respiratory failure, which translates to mean VT less than or equal to 6.5 ml/kg PBW in patients with ARDS (Figures E1A and E1B). Similarly, 15 sites had more than 30% of patients with acute respiratory failure receiving VT greater than 8 ml/kg PBW (Figure E1B), which also translated to a greater proportion of patients with ARDS receiving VT greater than or equal to 8 ml/kg PBW. Initial ventilator settings tended to persist over time, with little change in average VT over the first 3 days of mechanical ventilation. Among the 1,273 patients with VT greater than 6.5 ml/kg PBW who had ventilator data past the first day, only 311 patients (24.4%) had a reduction in VT to less than or equal to 6.5 ml/kg PBW on at least one subsequent day. In the LOTUS-FRUIT cohort, LTVV was more frequently used in sicker patients with conditions associated with higher mortality (such as ARDS and acute hypoxemic respiratory failure), and, unsurprisingly, in unadjusted analyses, LTVV was associated with worse outcomes (higher mortality, longer hospital length of stay, and lower VFD) (Table E2).

Simulation Model

In our calculation of expected clinical benefit from lowering VT to 6 ml/kg PBW, we modeled data from each of PRoVENT, the ARDSNet VT trial, and the LOTUS-FRUIT cohort. The multivariate model for mortality and the inverse probability propensity score model in the LOTUS-FRUIT cohort is shown in Tables E3 and E4. Most models demonstrated a negligible to small estimated mortality benefit from reducing VT from the observed VT of 7.1 ml/kg PBW to 6 ml/kg PBW (Table E5). The PRoVENT linear model and the ARDSNet VT trial linear logistic regression suggested an estimated 2% absolute mortality improvement with implementation of LTVV (2.1% and 1.5%, respectively). The PRoVENT spline model and the LOTUS-FRUIT inverse probability–weighted models suggested minimal to no estimated mortality benefit.

We also explored the possibility of using VFD as the primary outcome in the proposed LOTUS trial. Using the ARDSNet VT trial data, an estimated benefit of 0.34 VFD was suggested with lowering VT at LOTUS sites to 6 ml/kg PBW. Although the minimal clinically important difference of VFD has not been established, we deemed the benefit of 0.34 days too small to use VFD as an outcome in the LOTUS trial.

We used the maximal mortality benefit (2%) found by our modeling of the PRoVENT, ARDSNet trial, and LOTUS-FRUIT study in the simulation. Under these assumptions, a 4-year trial within the PETAL Network would enroll approximately 107,373 patients on the basis of event rates observed in LOTUS-FRUIT to have a 96% power to detect a 3% improvement in mortality at 80–100% adherence to LTVV (Table 2). Because some of the PETAL Network hospitals already demonstrated high adherence to LTVV in patients with acute respiratory failure, we considered the potential mortality difference that could be achieved if we were to exclude sites with already high adherence to LTVV from the proposed LOTUS trial. If the number of sites with high adherence to LTVV were excluded, there would be an increase in the estimated mortality benefit (Figure 1). With the increase in estimated mortality benefit, exclusion of sites with the highest adherence to LTVV in acute respiratory failure could potentially preserve

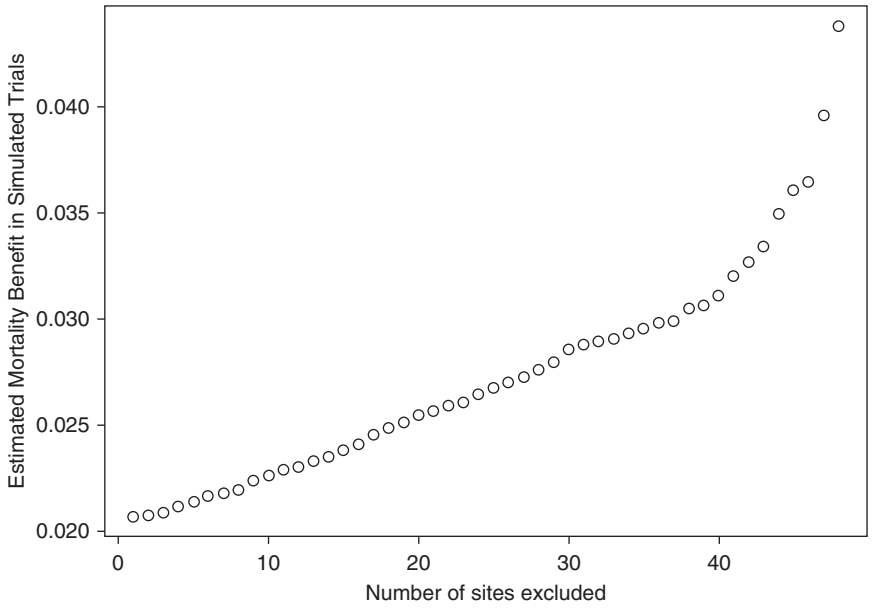

Figure 1. Estimated mortality benefit detectable in a stepped-wedged cluster-randomized controlled trial of low–tidal volume ventilation as sites with highest adherence to low–tidal volume ventilation less than or equal to 6.5 ml/kg predicted body weight are excluded from the trial.

power while decreasing the total number of patients in the trial (Table 2). However, even with exclusion of 20 sites (or 40% of the PETAL Network), 66,366 patients at 80% adherence to LTVV would be required to detect a significant mortality benefit with 86% power.

The budget for the observational LOTUS-FRUIT study to collect data on patients with acute respiratory failure was $215/patient. The data collection costs for the proposed LOTUS trial were expected to be significantly higher. Even assuming the same per-patient cost, an interventional trial would have cost over $23 million for 107,373 subjects from all sites or over $14 million for 66,366 patients from 29 sites with the highest usual V_T use in the PETAL Network. The PETAL steering committee thus deemed the LOTUS trial infeasible within the PETAL Network.

Discussion

LOTUS-FRUIT demonstrated that many PETAL Network patients with acute respiratory failure were already being managed with LTVV at a mean of 7.1 ml/kg PBW. This V_T is lower than the mean of 7.6 ml/kg PBW reported for patients with ARDS in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG-SAFE) (21). The use of LTVV, though low, is not universal. A notable proportion of patients may still benefit from implementation of LTVV, because 21% of patients with ARDS had an initial V_T greater than 8 ml/kg PBW.

The use of lower V_T within the PETAL Network sites may reflect several factors. First, PETAL Network sites in this study may be more attentive to V_T. Second, a change in general practice may explain the observations, especially after the publication of LUNG-SAFE and other studies demonstrating underuse of LTVV in ARDS. Last, we cannot exclude a "Hawthorne effect" whereby the knowledge that V_T would be measured in anticipation of the LOTUS trial resulted in increased use of LTVV at PETAL sites.

Despite the aforementioned evidence for LTVV in ARDS, the data are less compelling for LTVV in patients without ARDS. Because we observed similar V_T between patients with ARDS and patients without ARDS, this suggests that overall practice in PETAL hospitals has changed in the direction of LTVV, even for patients without ARDS, and it suggests some other drivers of LTVV besides ARDS. It is possible that these hospitals have already embraced or defaulted to, albeit incompletely, LTVV for respiratory failure, either by clinician choice or by protocol. Because many patients without ARDS also had risk factors for ARDS, it is possible that clinicians at these study hospitals may select LTVV for patients with respiratory failure and some risk factor for ARDS, given the mounting studies suggesting a potential benefit of LTVV in patients without ARDS (9–12).

It is uncertain how generalizable LOTUS FRUIT may be outside the PETAL Network. It is possible that a study might be more feasible in centers that use higher V_T. The LUNG-SAFE study observed average V_T of 7.6 ml/kg PBW, suggesting that usual practice at PETAL sites is not the same as usual care outside PETAL sites (21). Calculating what threshold of V_T would result in a feasible study is largely dependent on the model used for simulation. For example, if one designed a model solely on the basis of a linear interpolation of ARMA (the ARDSNet Lower Tidal Volume Trial), an average V_T of 7.8% would require a trial of about 7,000 patients. However, the datasets of PRoVENT and LOTUS-FRUIT suggest that 8 ml/kg PBW is about as good as 6 ml/kg PBW.

In the simulation of expected clinical benefit, we used models that assumed a linear relationship between changes in V_T and mortality and VFD. It is possible that the relationship is not linear. However, a nonlinear model of the PRoVENT data did not suggest any clinical effect of lowering V_T from usual care to LTVV. LOTUS-FRUIT and PRoVENT are observational cohorts in which the relationship between V_T and clinical outcomes may be confounded by multiple factors. Indeed, in this study, LTVV was associated with worse outcomes. Although we applied inverse probability of treatment weighting, there is likely to be residual confounding by indication. Nevertheless, even using the most generous estimate for an effect size in the proposed LOTUS trial, this simulation study suggested that an unfeasibly large trial would be required. In addition, the propensity model excludes commonly assessed measurements such as positive end-expiratory pressure (PEEP) and $F_{I_{O_2}}$, because they are set at the same time as the V_T (instead of before the decision to set V_T) and adjusted on the basis of oxygenation. Therefore, inclusion of lung compliance, PEEP, or many lung injury scores may not be straightforward. A more nuanced causal model that includes these factors and changes in V_T was beyond the scope of this study, given the time constraints of designing an interventional trial.

We note a prior report which demonstrated that the hazard of death for patients on mechanical ventilation was reduced by 23% for each 1 mg/kg reduction of V_T using a proportional hazards model with time-varying covariates representing other ventilation parameters and patient characteristics (14). However, this study was done only in patients with ARDS, and, because it only examined death during mechanical ventilation using proportional hazards models, it could not account in the denominator for patients who were extubated. Therefore, this reduction in hazard does not translate into a mortality difference to use in our simulation. For these reasons, we sought other cohorts and analysis looking at inpatient mortality as a binary outcome to estimate the possible improvement of mortality that might occur in our study.

The use of a simulation study has several advantages. Rather than estimating trial parameters from other practice settings and without attention to correlations within or between sites, we were able to employ empirically observed data, which are more likely to correspond with what will be seen during an actual trial. Similarly, we can design and power the study using accurately obtained clinical outcomes. A simulation study also allowed for the determination of the decrease in power associated with protocol nonadherence, thus providing an indication of what adherence levels to target in a pragmatic trial. Observational simulation studies can characterize care in the study hospitals to improve design and interpretation of the main interventional study, including generalizability. In addition, we could simulate trials with different combinations of sites and durations to determine the effect on power. Many clinical trials are underpowered and costly (22, 23). Feasibility studies such as this allow investigators to avoid investing limited resources in an underpowered trial. However, many of the costs of a large pragmatic trial like LOTUS could be reduced with automated data extraction and validation and by embedding study protocols into the electronic health record (24, 25).

The dissemination of LTVV from ARDS to all patients with acute respiratory failure in many hospitals is apparent from this study, implying that LTVV is well tolerated even in patients without ARDS in some centers. Although there have been some trials of LTVV in patients without ARDS, none have definitively demonstrated a mortality benefit. Such trials have been either nonblinded before-and-after trials (26) or trials that exposed the control arm to V_T above what is employed in usual care, thereby decreasing the external validity of these results (9, 12, 27). In contrast, LOTUS was designed to be a pragmatic trial with usual care as the control. The control strategy motivated LOTUS-FRUIT to determine usual-care practice and model its effect on trial power and feasibility. The window for such a trial comparing LTVV with usual care may be closing as more sites adopt LTVV for acute respiratory failure. Careful selection of sites with clear definition of baseline usual practice and innovative strategies for low-cost large pragmatic trials will be needed for such a trial.

There are some limitations to our approach. First, we measured V_T at discrete times rather than continuously, assuming minimal change in the V_T over the course of the day. Height, and therefore PBW, was missing in 11% of patients, but this likely reflects the current state of medical documentation. The expected clinical benefit from lowering the V_T from usual practice to 6 ml/kg PBW was extrapolated by assuming linearity from previous trials (1, 19). The true relationship between V_T and mortality may not be linear, but our spline model did not suggest efficacy. Last, although a pragmatic cluster-randomized controlled trial was not feasible within the PETAL Network, it may still be feasible in sites in which LTVV is less common or automated data extraction can be performed.

Conclusions

In preparation for a stepped-wedged, cluster-randomized controlled trial of LTVV we found that the planned trial was infeasible within the PETAL Network, in large part because many centers already practice LTVV in patients with acute respiratory failure (overall mean V_T of 7.1 ml/kg PBW). This or a similar method may help avoid the launch of infeasible trials in the future that would have a low likelihood of being able to test the primary hypothesis. ■

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