Protocol Title: Lung-protective ventilation initiated in the emergency department to reduced ventilator-associated conditions and acute respiratory distress syndrome
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I. Abstract

Ventilator-associated conditions (VACs) represent progressive pulmonary organ failure in mechanically ventilated critically ill patients. VACs are common, and if caused by acute respiratory distress syndrome (ARDS) have a mortality rate of approximately 40%; they are a leading contributor to death in critically ill patients. Survivors also experience prolonged physical and mental disability. The Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) are viewing VACs as a quality measure for the management of mechanically ventilated patients and comparing outcomes between hospitals. The high mortality rate, lack of treatment options, and morbidity experienced by survivors suggests that **prevention of VACs** may be the most effective strategy. VACs develop in a significant percentage of patients shortly after admission, and can therefore be viewed as a time-sensitive emergency. The **emergency department** (ED) is the entry point for many of the highest risk patients for VACs, yet remains a relatively unstudied location with respect to the prevention or mitigation of their occurrence. As ventilator-associated lung injury (VALI) has been shown to occur during the first few hours of mechanical ventilation, a preventive intervention in the ED, targeting these high risk patients, could be the systematic program that is needed to improve outcome.

Cyclic alveolar over distention from positive pressure ventilation is a key element in the pathogenesis of lung injury. VALI promotes inflammatory injury and can cause VACs in healthy lungs. **Lung-protective ventilation**, by limiting VALI, reduces mortality in critically ill mechanically ventilated patients. Observational data and a small randomized trial suggest that non-lung-protective ventilation, implemented early in the course of respiratory failure, is associated with the progression to VACs in previously non-injured lungs. Our preliminary data shows that the early use of potentially injurious ventilation is common in ED patients, and that progression to VACs is frequent and occurs shortly after admission from the ED. Early initiation of lung-protective ventilation in the ED may therefore be an effective VAC preventive strategy and has become the standard approach to ventilation in the ED at BJH. Preventing VACs by studying and intervening in high risk ED patients has not been a previous research target however. Since progression to VACs is a time-sensitive emergency, targeting this pre-intensive care unit (ICU) environment may be the most promising window of opportunity to prevent these complications.

To test our hypothesis, we propose the following **specific aim:**

1. To determine whether initiating lung-protective ventilation in the ED will result in fewer pulmonary complications in mechanically ventilated patients when compared to pre-intervention historical controls. In a quasi-experimental, before-after study, we will evaluate the effect of lung-protective ventilation on the development of ARDS and VACs.

II. Background and Significance/Preliminary Studies

A. Significance

VACs negatively impact public health.
VACs are common. Due most commonly to ARDS and ventilator-associated pneumonia (VAP), they affect over 200,000 patients annually in the United States.[1-3] The incidence of VACs currently exceeds other high profile diseases, such as cerebrovascular disease, Alzheimer's disease, influenza, and chronic liver disease.

VACs are deadly. VACs due to ARDS are a leading cause of death in critically ill patients, with a mortality rate of ≈40%, and high as 60% in some cohorts.[1] Mortality in patients developing a VAC is almost 5-fold higher (65.7%) compared to patients that do not develop a VAC (14.4%).[3]

VACs are costly. A minority of VAC survivors are discharged to home; they suffer long-term sequela, including cognitive decline, psychological dysfunction, and lengthy rehabilitation.[1, 2] VACs increase ventilator days, and account for millions of hospital days each year.[1, 4] The public health impact is profound.

Ventilation strategy is a major risk for the development of ventilator-associated lung injury (VALI).
Animal models have established that the mechanical ventilator can injure lungs; this injury is decreased by using lung-protective ventilation. [5-10]

Human data has established that lung-protective ventilation reduces mortality. Three randomized controlled trials (RCT) demonstrate that lung-protective ventilation reduces mortality in critically ill mechanically ventilated patients.[11-13] This remains the only consistent beneficial therapy across syndrome severity in ARDS.

Observational data and two RCTs show that lung-protective ventilation reduces pulmonary complications.[14-21] These clinical data suggest a causal link between injurious ventilation and incidence of VACs in critically ill patients without injured lungs at the time of initiation of mechanical ventilation.

B. Innovation

Two novel targets: The ED and VAC prevention.
Several lines of evidence suggest that early intervention in the ED is key to the prevention of VACs. With over 100 million visits annually and increasing lengths of stay before inpatient admission, critical care is provided in the ED more than ever.[22, 23] These patients stay in the ED for over 6 hours or more, resulting in 154 patient-days of annual critical care provided.[24-27] This transfer delay to the ICU increases mortality, suggesting that treatment and prevention be initiated immediately.[28] The need for ventilation has shown a parallel increase in the ED, and longer ED lengths of stay are associated with mortality and resource expenditure.[29, 30]

Time is critical. Animal data, supported by human data from the operating room, suggest that mechanical ventilation promotes lung injury and organ dysfunction in minutes to hours.[10, 31-34] Acute progression of VALI, combined with increasing use of mechanical ventilation in the ED, suggests that respiratory failure in the ED is in need of a high impact intervention for the prevention of VACs. Prior to our research, no mechanical ventilation studies had been conducted in the ED - this is a substantive departure from the status quo.

Treatment of pulmonary complications is the status quo. Research in mechanically ventilated patients has classically focused on therapies aimed at treatment after onset.[35] Unfortunately, the number of failed clinical trials far exceeds trials demonstrating benefit.[35] The use of preemptive lung-protective ventilation represents the novel application of *preventive* therapy.

i.Preliminary Data

Lung-protective ventilation is uncommon in ED patients and is delivered for prolonged periods.
In 251 patients with sepsis, only 27.1% received lung-protective ventilation.[36] There was high variability of tidal volume (5.2-14.6 mL/kg PBW), and injurious levels were common. Patients were exposed to prolonged ventilation times, with a 5.5 hour median ED length of stay (IQR 4.2-7.5).

Pulmonary complications after ED admission are a significant problem.
Focusing on the subset of VACs due to ARDS, our data found that progression to ARDS occurred in 27.5% of patients.[36] To put our data in context, we conducted a systematic review (n= 1,704 studies), which revealed similar findings.[37] ARDS progression rate was 6% to 44% after ICU admission. Patients experiencing these complications had increased mortality, lengths of stay, mechanical ventilation days, and organ failure.[37] These data are significant by showing that VACs after ED admission are a serious problem, and the timing of onset suggests a temporal relationship to treatment delivered in the ED. Finally, based on this rigorous systematic review, we can definitively say that no ED-based mechanical ventilation studies (outside of our work) have been conducted. This represents a significant knowledge gap.

Initial care provided in the ED is influential on outcome and subsequent care.

The care provided in the ED in large part determines overall outcome in time-sensitive emergencies, such as stroke and sepsis.[38, 39] Our previous work has shown that ED antibiotic dosing determines subsequent inpatient dosing.[40] Expanding on that paradigm, our ventilator data shows that ventilator settings were continued unchanged in 24.8% of patients.[36] This suggests that an early lung-protective ventilation strategy would improve care both in the ED and ICU.

Early lung-protective ventilation can reduce pulmonary complications.
Our systematic review revealed that injurious ventilation was an independent predictor for worsening pulmonary failure.[37] Two RCTs in the ICU and operating room reached similar conclusions. [20, 21]

Mechanically ventilated ED patients can be prospectively studied. (ClinicalTrials.gov ID NCT01628523) In a multicenter prospective study, we have accrued more data pertinent to this proposal: (1) protective ventilation remains uncommon in the ED, and extends beyond our center (unpublished data); and (2) many ED patients are ventilated and it is feasible to capture and study them early. Based on this analysis, we can say that mechanical ventilation in the ED is delivered using: 1) higher than recommended tidal volumes and infrequent lung-protective ventilation; 2) excessive oxygen and low positive end-expiratory pressure (PEEP); and 3) the supine, flat position. These data show a major window of opportunity for VAC prevention by targeting the ED.

Research interventions must be generalizable.
There is hesitancy to adopt critical care interventions requiring significant resources.[41] In a survey of emergency and critical care physicians, we assessed the willingness to adopt ED lung-protective ventilation. Only 25% of physicians felt there was adequate data to guide ED management of mechanical ventilation. There was 100% willingness to adopt lung-protection in the ED to prevent complications [42]. Our work has generated significant interest in the critical care community, suggesting study results showing benefit from a relatively simple intervention would be widely adopted, potentially saving lives and dollars.[43-45]

The candidate has access to a high volume of mechanically ventilated patients.
Our ED evaluated >95,000 patient visits in 2013, and 1.9 patients per day receive mechanical ventilation. Our robust, automated, electronic screening method has demonstrated that we can capture every mechanically ventilated patient in the ED. These estimates are an assurance of project feasibility.

III. Study Aims

Clinical outcomes: The primary outcomes of interest are the development of VACs and ARDS after admission the hospital. VACs will be analyzed until day 14, as preliminary data suggest that the great majority of VACs develop within this time period[3]. ARDS will be analyzed until day 7, as preliminary data suggest that the majority of ARDS cases will develop within this time period [36, 37, 46]. We hypothesize that the initiation of lung-protective ventilation in mechanically ventilated ED patients is associated with a decrease in VACs when compared to historical controls.
Secondary outcomes will be assessed and include: adherence to lung-protective ventilation in the ED and ICU, correlation between ED and ICU tidal volume, early reversal of organ failure (SOFA scores), mechanical ventilation duration, vasopressor duration, lengths of stay (ICU and hospital), mortality. Going forward, other secondary, long-term outcomes will be assessed and include: quality of life, cost, functional status, need for re-admission, neurocognitive function.

IV. Administrative Organization

The present investigation will be conducted in the ED of Barnes-Jewish Hospital in St. Louis, MO. Patients will be followed in the ED and the ICU for data and clinical outcomes. Data management and statistical coordination will be performed by the principal investigation (B Fuller) and research assistant.

V. Study Design

To test the hypothesis that lung-protective ventilation in the ED is associated with a reduced rate of VACs and ARDS, we have designed a quasi-experimental, prospective observational, before-after clinical study. An outline of the study design and study procedures appears in **Figure 1 and Figure 2**.

Adult patients aged 18 years and older, receiving mechanical ventilation via an endotracheal tube will be enrolled. Exclusion criteria include: 1) death within 24 hours of presentation; 2) discontinuation of mechanical ventilation within 24 hours of presentation; 3) chronic mechanical ventilation; 4) presence of a tracheostomy; 5) transfer to another hospital from the ED; and 6) fulfillment of ARDS criteria at hospital presentation.
Patients will be recruited exclusively from BJH ED. Based on the demographics of the patient population routinely presenting to BJH, the resulting study population is expected to be diverse and representative of the general population of critically ill patients at risk for VACs and ARDS, such that the study findings can be externally validated and generalizable to the broader community as whole.

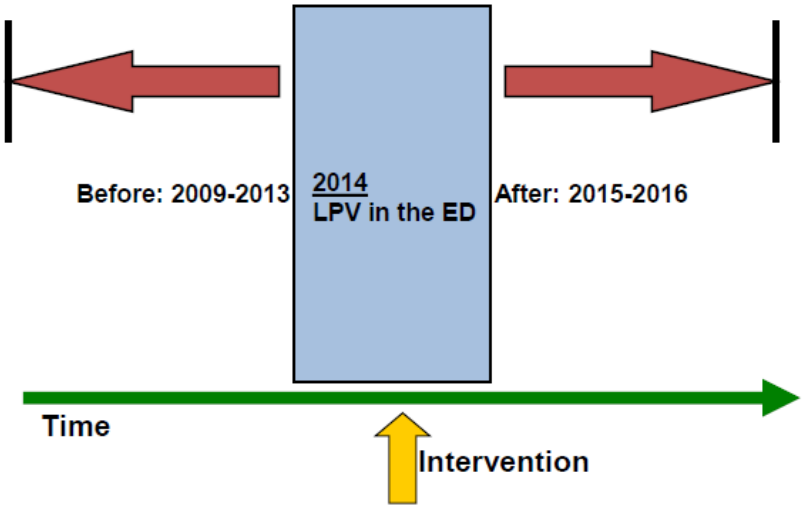
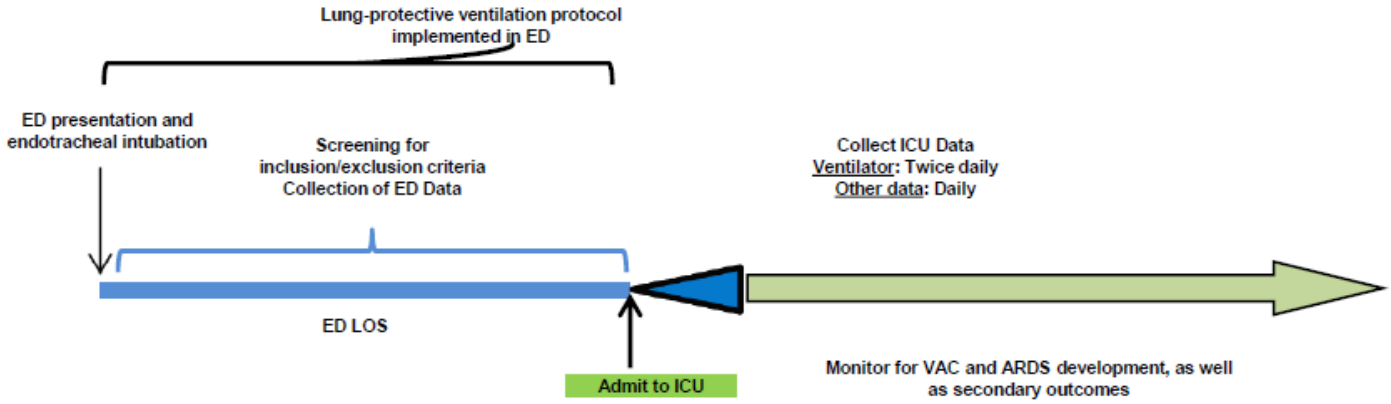


Figure 1. Schematic of before-after trial design
LPV: lung-protective ventilation; ED: emergency department

VI. Study Procedures

Subjects will be screened in the ED at BJH. Those fulfilling inclusion and exclusion criteria (see above) will be enrolled in the study. Lung-protective ventilation is the current default approach to mechanical ventilation in our ED. This will therefore be an observational study and informed consent is not required. After leaving the ED, mechanical ventilation management will continue at the discretion of the treating clinician.



Patients will be screened for inclusion in the ED. To facilitate this screening, an automated, electronic pager system is in place (CASE-ED), which screens patients 24 hours/day, 7 days/week. To capture mechanically ventilated patients for the purpose of this study, it has been programmed with the following triggers: 1) receipt of a paralytic drug; 2) an order for mechanical ventilation parameters; and 3) an intubation procedure note.

We will take a pragmatic approach to the study design, and therefore co-interventions which may influence the event rate for the primary outcome (e.g. antibiotics and fluid management) will not be standardized, and will be at the discretion of the treating clinician. We will statistically analyze potential differences in baseline characteristics and process-of-care variables between the before and after groups. While this introduces risk of an imbalanced cohort for comparison, and therefore potential to limit the ability to detect an effect of the

intervention, we have chosen this approach: 1) to maximize generalizability to the community as a whole; 2) because no systematic differences in care (excluding lung-protective ventilation) have been introduced in the ED at BJH which may influence the event rate of interest.

Additional conditions and variables of interest in the ED include: baseline demographic characteristics, co-morbid conditions, illness severity scores, vital signs and laboratory data, and ED process-of-care variables, including all mechanical ventilator data.
After admission to the ICU, all ventilator data will be recorded twice daily (A.M. and P.M.). Once daily ICU data will include: RASS and CAM-ICU scores, daily fluid balance, and receipt of transfusion.
A full schedule of events for this study protocol can be seen in **Table 1**.

Table 1 Schedule of events

Event	ED presentation and endotracheal intubation	LPV protocol initiated by RTs	ICU Admit Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8-14	Hospital discharge or study Day 28, whichever comes first	6 months	12 months
Inclusion/exclusion criteria	X												
Demographics	X												
Co-morbidities	X												
Illness severity scores	X												
Vitals and lab data	X												
ED treatment variables	X												
ED ventilator data	X												
ICU ventilator data (twice daily)			X	X	X	X	X	X	X	X			
SOFA Score			X	X									
RASS Score			X	X									
CAM-ICU			X	X									
Fluid balance			X	X	X	X	X	X	X	X			
Transfusion			X	X	X	X	X	X	X	X			
ARDS Outcome			X	X	X	X	X	X	X	X			
VAC Outcome						X	X	X	X	X			
Mortality											X		
Other secondary outcomes											X		

VII. Safety Monitoring Plan

Human subjects involvement and characteristics: This research will be performed in ED and ICU patients only. Subjects meeting eligibility criteria will be enrolled in this prospective cohort study outlined in the Research Plan. As this study is observational in nature, comparing evolving treatment standards over time, it will be conducted under waiver of informed consent. The number of subjects (n = 513) in the proposed study is based on sample size estimates performed with assumptions from preexisting clinical studies and our preliminary data. Patients, eighteen years of age or older, requiring intubation for respiratory failure and not meeting exclusion criteria will be studied. This patient group is the optimal population to test lung-protective ventilation for the prevention of VACs.

Sources of material: This study does not require the acquisition of clinical data specifically for research purposes. We will use data from the index hospitalization only. No follow-up visits or prolongation of length of stay will be required. Data will be used for research purposes, and all of the data to be collected is also used for the clinical management of the patient as part of routine clinical practice. All protected health information (PHI) will be de-identified in a HIPAA-compliant fashion when a case is entered into the study database. The PI

will be the only person with access to the source code linking PHI to the data, and this source code will be kept in a locked cabinet in the PI's private office.

There are no procedures performed just for research purposes, as this is an observational study.

Potential Risks: The potential risks include: (1) potential breach of confidentiality.

Protection Against Risk: The risk of loss of confidentiality will be minimized by the storage of all case report forms in a locked cabinet in the PI's locked private office. Data will be transferred to a password-protected computer that is encrypted per university policy, and it will be stored in a de-identified state (i.e. subjects will be assigned a unique study code). Once follow-up is complete for each subject, all identifier data is deleted so that the only link between the study case number and PHI will be the paper roster stored in a locked cabinet in the PI's office. The PI will ensure that the anonymity is maintained. Patients will not be identified by name in any reports on this study. All records will be kept confidential to the extent provided by federal, state, and local law.

VIII. Analysis Plan

There are two cohorts of interest: 1) a pre-intervention group, prior to the implementation of a lung-protective ventilator protocol; and 2) a post-intervention group managed with a ventilator protocol as described above, and in Figure 2. Categorical characteristics will be compared using the chi-square test or Fisher's exact test. Continuous characteristics will be compared using the independent samples t-test or Wilcoxon's rank-sum test. The primary analysis will compare the proportion of patients in each cohort with and without the occurrence of pulmonary complications (e.g. ARDS or VACs) using logistic regression with propensity-score (PS) adjustment. Multivariable logistic regression will be used to derive the PS, with cohort as the dependent variable. Cohort 2 patients will be categorized into quintile subclasses based on their ranked estimated PS and then matched to cohort 1 patients to achieve a similar distribution of covariates. Unmatched cases in cohort 1 will be discarded. Simple diagnostics and linear regression testing for a quintile by cohort interaction will be used to verify balance, and if not achieved, PSs will be re-estimated using transformations or interactions. In final logistic regression, the treatment effect is defined as the odds of pulmonary complication as a function of cohort, with adjustment for the quintiles of the PS. Development of ARDS and VACs will also be analyzed separately. Secondary outcome variables will be compared using PS-adjusted logistic regression (mortality) and PS-adjusted Poisson regression (lengths of ICU/hospital stay, mechanical ventilation days). We will conduct *a priori* subgroup analyses to further understand the treatment effect and identify subgroups in which heterogeneous treatment effects exist. These subgroups include (but are not limited to): sepsis, trauma, neurologic injury, and presence of shock. Missing data will be handled by multiple imputation methods. Upon study completion, other statistical methods will be explored as necessary, and all analyses will be conducted in consultation with a biostatistician.

The sample size is calculated for the primary outcome, the development of pulmonary complications. We expect an event rate of approximately 20% in the before group. As a reflection of a decrease in VALI, we expect an absolute risk reduction of 5.4% for pulmonary complications in the after group. This will require a total sample size of post-intervention subjects of 513 to have 80% power. All tests will be two-tailed, and a P value <0.05 will be considered statistically significant.

IX. Literature Cited

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