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Supplementary appendix

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Effect of a fluid bolus on cardiovascular collapse in critically ill adults undergoing tracheal intubation: A randomized clinical trial

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Supplemental Methods

A. Study Interventions

The PrePARE trial aimed to only affect the initiation of fluid bolus administration prior to induction for the prevention of cardiovascular collapse between induction and two minutes after completion of tracheal intubation. The study did not affect fluid administration initiated prior to enrollment, fluid administration initiated two minutes after completion of intubation, or fluid bolus administration for the treatment of cardiovascular collapse. This study did not protocolize any other aspect of tracheal intubation such as choice of induction agent and neuromuscular blocker, patient position, choice of laryngoscopy – all of which were determined by the treating clinicians.

Once the randomization envelope was opened and group assignment was known, the clinical team initiated a fluid bolus (fluid bolus group) or did not initiate a fluid bolus (no fluid bolus group) prior to the administration of procedural medications. If difficulties with airway management were encountered, the provider could revise the fluid management strategy at any time thereafter in order to ensure safe performance of the procedure.

For patients randomized to the fluid bolus group (**figure A**), the bedside nurse obtained 500 milliliters of a isotonic crystalloid solution of the operator's choosing, connected this volume to intravenous infusion tubing, and attached the tubing to any intravenous catheter or intraosseous access. The crystalloid fluid was then placed above the level of the intravenous or intraosseous access and infused by gravity and bag pressure. At any time after the initiation of the fluid bolus, the operator could choose to begin the intubation procedure by administering procedure-related medications. The fluid bolus was continued until all 500 milliliters were infused. Infusions present prior to the decision to perform tracheal intubation were not altered by the study.

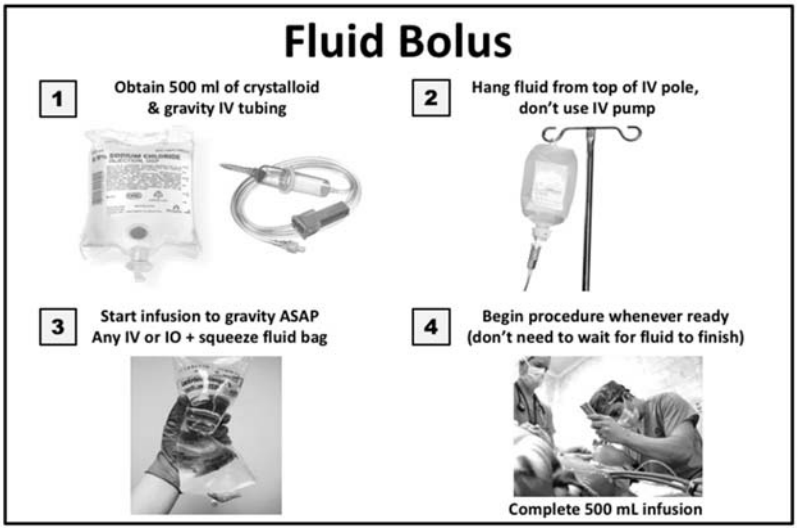


Figure A. Instructions provided to the bedside clinical team for patients randomized to the fluid bolus group

In patients randomized to the no fluid bolus group (**figure B**), no additional intravenous crystalloid administration was initiated by the study between enrollment and two minutes after completion of tracheal intubation. Infusions present prior to the decision to perform tracheal intubation were not affected by the study and their management was deferred to the treating clinician. Treating clinicians could initiate a fluid bolus at any time for the treatment of cardiovascular collapse (not considered a protocol violation). Treating clinicians could also initiate a fluid bolus at any time if felt to be required for the safe treatment of the patient (if between enrollment and two minutes after completion of intubation and in the absence of cardiovascular collapse this was recorded as a protocol violation).

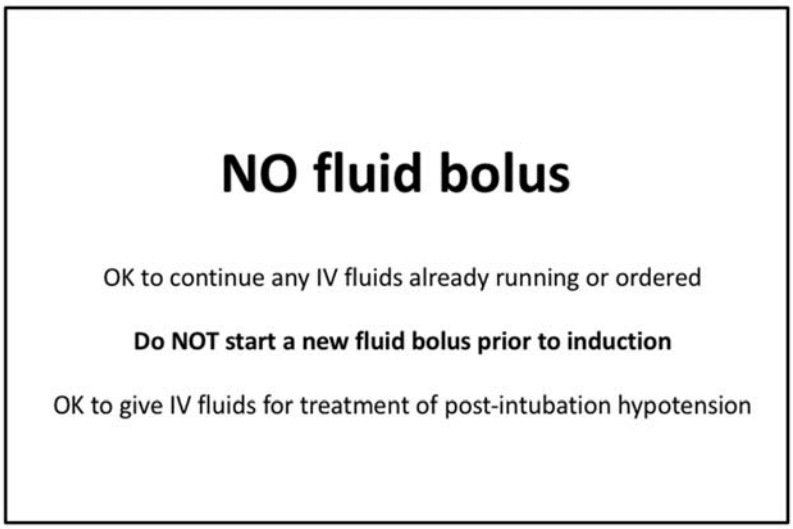


Figure B. Instructions provided to the bedside clinical team for patients randomized to the no fluid bolus group

B: **Sample Size Calculation and Summary of Statistical Analysis Plan**

Power and Sample Size

In a previous before-and-after observational study [1] which incorporated a preemptive intravenous fluid bolus to prevent cardiovascular collapse during tracheal intubation in critically ill adults, the incidence of cardiovascular collapse was approximately 25% in the before fluid bolus period and 15% in the after fluid bolus period (an absolute risk reduction of 10% and a relative risk reduction of 40%). Randomization of a total of 500 patients (250 patients per group) would provide 80% power to detect the same 10% difference in cardiovascular collapse between groups with a two-sided alpha of 0.05. Sample size calculation was performed using PS: Power and Sample Size Calculation version 3.1.2, 2014.

Statistical Analysis Plan

The statistical analysis plan, below, was made publicly available prior to the completion of enrollment and can be found at:

https://rocket.app.vumc.org/index.php?doc_id=20364

Analysis principles

- Primary analysis will be conducted on an intention-to-treat basis (patients with protocol violations are analyzed per the assigned treatment arm).
- All hypothesis tests will be two sided, with an α of 0.05 unless otherwise specified.
- All analyses will be unadjusted unless otherwise specified.
- Subgroup analyses will be performed irrespective of treatment efficacy.

Trial profile

We will present a Consolidated Standards of Reporting Trials diagram to detail the movement of patients through the study. This diagram will include total number of patients meeting inclusion criteria, number excluded and reason for exclusion, number enrolled and randomized in the study, number followed, and number analyzed.

Baseline comparisons and assessment of randomization

To assess randomization success, we will summarize in a table the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges. Variables reported will include Demographics (age, gender, race, BMI, co-morbidities); Indication for intubation; Active illnesses at the time of intubation; Severity of Illness (APACHE II score); Respiratory status pre-intubation; vasopressor use at the time of intubation; Airway management procedure (Preoxygenation technique, systolic blood pressure at time of induction, Induction medication, Neuromuscular blocker, Laryngoscope type).

Primary Analysis

Unadjusted test of treatment effect. The primary analysis will be an intention-to-treat, unadjusted comparison of the primary outcome between patients assigned to the fluid loading and no fluid loading groups. The primary endpoint will be the categorical variable of cardiovascular collapse. The difference between the two groups will be compared using the $\chi 2$ test.

Secondary Analyses

Analysis of Secondary and Exploratory Outcomes. We will conduct unadjusted analyses examining the treatment effect of fluid loading on each of the pre-specified secondary and exploratory outcomes. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the $\chi 2$ test. Kaplan-Meier curves and log-rank tests will be used to analyze time-to-event comparisons between groups.

Primary Outcome

- Cardiovascular collapse, defined as one or more of the following:
  - Death within 1 hour of intubation
  - Cardiac arrest within 1 hour of intubation
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
  - New or increased vasopressor between induction and 2 minutes following intubation

Secondary Outcomes

- Each component of the cardiovascular collapse composite:
  - Death within 1 hour of intubation
  - Cardiac arrest within 1 hour of intubation
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
  - New or increased vasopressor between induction and 2 minutes following intubation

Exploratory Outcomes

1. Cardiovascular collapse composite outcome with an alternate systolic blood pressure cutoff:
   i. Death within 1 hour of intubation
   ii. Cardiac arrest within 1 hour of intubation
   iii. New systolic blood pressure < 90 mmHg between induction and 2 minutes following intubation
   iv. New or increased vasopressor between induction and 2 minutes following intubation
2. Incidence of systolic blood pressure < 90 mmHg between induction and 2 minutes after intubation
3. Lowest systolic blood pressure between induction and 2 minutes after intubation
4. Change in systolic blood pressure from induction to lowest systolic blood pressure
5. Lowest arterial oxygen saturation between induction and 2 minutes after intubation
6. Incidence of hypoxemia (oxygen saturation <90%) between induction and 2 minutes after intubation
7. Incidence of severe hypoxemia (oxygen saturation <80%) between induction and 2 minutes after intubation
8. Incidence of desaturation (defined by decrease in oxygen saturation of >3%) between induction and 2 minutes after intubation
9. Change in saturation from induction to lowest oxygen saturation between induction and 2 minutes after intubation
10. Lowest SpO_2 in the 6-24 hours after intubation
11. Highest FiO_2 in the 6-24 hours after intubation
12. Highest positive end-expiratory pressure in the 6-24 hours after intubation
13. Cumulative diuretic dose (in furosemide equivalents) from enrollment through three days after intubation
14. Cumulative intravenous fluid administration from enrollment through three days after intubation
15. Vasopressor receipt in the 1 hour after intubation
16. Composite of new or worsening shock in the 1 hour after intubation
    - New mean arterial blood pressure < 65 mmHg
    - New vasopressor use
    - Increased dose of previous vasopressor
17. In-hospital mortality
18. Ventilator-free days (VFDs)
19. ICU-free days (ICUFDs)

Measures of Study Intervention Delivery

Measures of study intervention will be presented for each study group but are not study outcomes:

1. Estimated volume of intravenous fluids infused as part of fluid loading prior to induction drug administration

Co-interventions

Co-interventions are aspects of the endotracheal intubation procedure that will be presented for each study group but are not study outcomes:

1. Time from administering induction medications to successful endotracheal intubation
2. Cormack-Lehane grade of view on first attempt
3. Incidence of endotracheal intubation on first attempt
4. Number of attempts required for successful tube placement
5. Incidence of need for additional intubating equipment, second operator
6. Agreement between primary and secondary outcomes recorded by observers and study staff

Per-Protocol Analyses. In addition to the intention-to-treat analysis, we will conduct a per protocol analysis of the primary outcome comparing patients who received fluid loading prior to induction compared to patients who received no fluid loading prior to induction.

Effect Modification (Subgroup analyses). We will determine whether pre-specified baseline variables modify the effect of treatment group on the primary outcome. We will evaluate for effect modification by fitting a logistic regression model for the composite primary outcome of cardiovascular collapse; independent variables will include study group assignment, the potential modifier variable of interest, and the interaction between the two (e.g., study_group*vasopressors at enrollment). Significance will be determined by the *P* value for the interaction term, with values less than 0.10 considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. Subgroups derived from categorical variables will be displayed as a forest plot. Continuous variables will be analyzed using restricted cubic splines with 3-5 knots and preferentially displayed as continuous variables with predicted probabilities of the categorical outcome. If the presentation of data requires it, dichotomization of continuous variables for inclusion in the forest plot will be performed.

Pre-specified subgroups that may modify the physiologic impact of fluid loading:

1. Vasopressor receipt at enrollment (Yes/No)
2. Baseline left ventricular ejection fraction (continuous variable)
3. Septic shock diagnosis in the ICU (Yes/No)
4. Congestive heart failure diagnosis at baseline (Yes/No)
5. Chronic kidney disease, including end-stage renal disease, diagnosis at baseline (Yes/No)
6. Cirrhosis diagnosis at baseline (Yes/No)
7. Non-invasive ventilation for preoxygenation (Yes/No)
8. Bag-mask ventilation after induction (Yes/No)

Subgroups related to risk for the primary outcome:

1. APACHE II score at enrollment (continuous variable)
2. Reason for intubation (Hypoxic or Hypercarbic Respiratory Failure / Altered mental status or seizure / Procedure / Other)
3. Lowest systolic blood pressure in the 6 hours prior to the procedure
4. Lowest SpO2 in the 6 hours prior to the procedure and at induction
5. BMI
6. Re-intubation
7. Induction agent (Etomidate / Propofol / Other)

Modeling to Examine Potential Confounding Factors. We will develop a logistic regression model with the primary outcome as the dependent variable and study group and relevant confounders included as

independent variables (age, APACHE II score, vasopressor receipt at induction, systolic blood pressure at induction).

Missing Data. In the initial analysis, missing data will not be imputed. As sensitivity analyses, the primary analysis will be repeated with missing data imputed by (1) assigning a value of "No, primary endpoint did not occur" to data missing from the fluid loading group and a value of "Yes, primary endpoint did occur" to data missing from the no fluid loading, and (2) assigning a value of "No" to data missing from the fluid loading group and a value of "Yes" to data missing from the no fluid loading group.

Corrections for multiple testing

We have pre-specified a single primary analysis of a single primary outcome. All additional analyses will be considered hypothesis-generating, and no corrections for multiple comparisons will be performed.

C. Interim Analysis

The DSMB conducted a planned single interim analysis for efficacy, safety, and futility at the anticipated halfway point of the trial, 30 days after enrollment of 250 patients. Enrollment continued during this period. The pre-specified **stopping boundary for efficacy** would have been met if the P value for the difference between groups in the primary outcome was 0·003 or less. Assuming a 25% incidence of cardiovascular collapse in the no fluid bolus group, this stopping boundary would have stopped the trial for any relative risk reduction greater than 58%. If the trial had not met this stopping point, but still had the same relative risk reduction for the second half of the patients enrolled, at most 18 additional patients would have been at risk for developing life-threatening cardiovascular collapse due to not stopping the trial early. Use of this conservative stopping boundary ($P \leq 0{\cdot}003$) would allow the final analysis to be performed using an unchanged level of significance ($P = 0{\cdot}05$).

The interim analysis by the DSMB also evaluated the trial for futility. A **futility stopping boundary** of $P > 0{\cdot}60$ when analyzing the intervention and control groups regarding the primary outcome was used for stopping the trial for futility. If the no fluid bolus group had the anticipated 25% incidence of life-threatening cardiovascular collapse, this means the trial would have been stopped for futility at the interim analysis if the relative risk reduction was 12% or less (equivalent to an absolute risk reduction less than 3%). The DSMB was provided data on the first 250 patients enrolled, the DSMB was blinded to study group assignment, and the DSMB calculated the p-value for the incidence of the primary outcome between study groups. With these data, the DSMB calculated the number of patients (proportion) with the primary outcome to be 27 (21·4%) in blinded group A and 26 (21·0%) in blinded

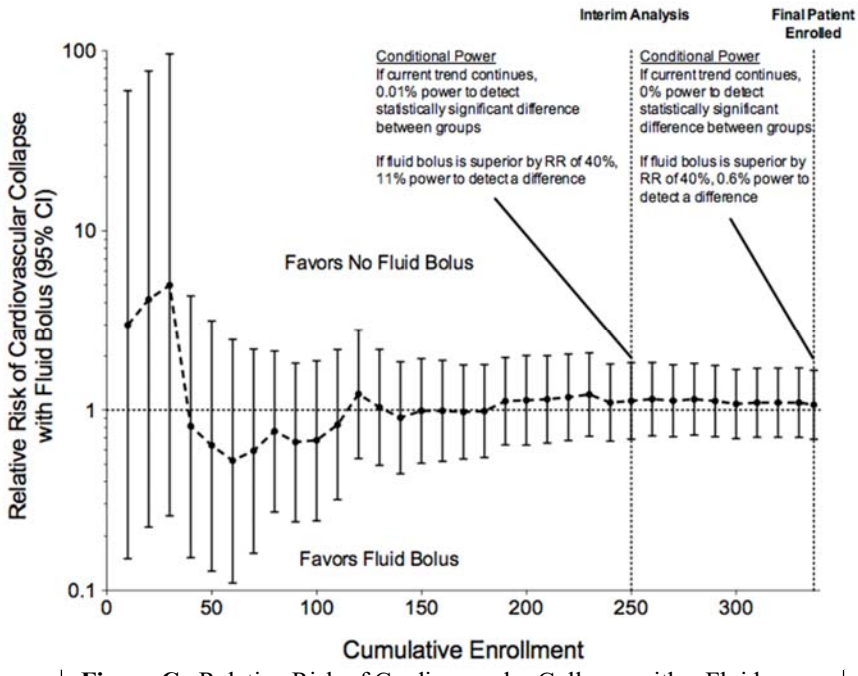


Figure C. Relative Risk of Cardiovascular Collapse with a Fluid Bolus as the Trial Progressed.

group B, with a p-value of 0·93. Given that this p-value met the prespecified futility stopping boundary of a p-value > 0·60, the DSMB recommended the trial be stopped and the investigators accepted that recommendation.

Based on a previous observational study, the trial began with the assumption that there would be a relative risk reduction of 40% in the incidence of cardiovascular collapse with a fluid bolus compared with no fluid bolus, and at the trial outset the trial had 80% power to detect this difference with a total sample size of 500. With the incidence of cardiovascular collapse in each group at the interim analysis of 250 patients, we calculated the conditional power of the trial to detect a statistically significant relative risk reduction of 40% if the trial would have continued to enroll 500 total patients (**Figure C**). Based on the results of the interim analysis, if the trial had continued to completion it would only have had 11% power to detect a 40% relative risk reduction in cardiovascular collapse with a fluid bolus. When calculating the conditional power of the trial using data from all 337 patients enrolled, the conditional power of the trial to detect a 40% relative risk reduction in cardiovascular collapse with a fluid bolus was 0.6% (software used to conduct the conditional power analysis: http://resourcetepee.com/free-statistical-calculators/conditional-power-calculator/).

With regards to safety, the DSMB was able to stop study accrual at any time if there was concern for safety. Other than these concerns, the DSMB was asked to formally evaluate the safety of the trial at the interim analysis. As the theoretical risk of the fluid loading intervention was acute pulmonary edema requiring increased ventilatory support, the primary determination of safety was based on the highest fraction of inspired oxygen and highest positive end-expiratory pressure between 6 and 24 hours after intubation. Although no safety issues arose during the trial and the safety stopping boundary was not met, the **safety stopping boundary** was as follows:

1. The *P* value for the difference between study groups in both of these physiologic variables is < 0.001, AND
2. The difference between groups in both physiologic variables is concordant in direction with the point estimate for in-hospital mortality, AND
3. The *P* value for the difference between study groups in in-hospital mortality is < 0.1

Finally, the DSMB had the ability to monitor the incidence of the primary outcome in the no fluid bolus group at the interim analysis and could ask that the study be re-powered if the incidence of the primary outcome was different from our original estimate of 25% to ensure that the study maintained an 80% power to detect a 40% relative risk reduction in the primary outcome.

D. Data Sharing Statement

Following publication and upon reasonable request, a completely de-identified data set and data dictionary with individual participant data may be provided by the authors. Request to share data from the PREPARE trial should be sent, along with a brief research proposal, to the principal investigator, David Janz, MD at djanz@lsuhsc.edu. The data set will be provided to researchers whose proposed use of the data has been approved by the steering committee and an Institutional Review Board.

Supplemental Tables

eTable 1. Study ICU Characteristics

Characteristic	Vanderbilt MICU	LSU UMCNO MICU	Ochsner MICU	UW MICU	UW NICU	UW TICU	Lahey MICU	UAB MICU	Lincoln ED
Annual admissions/visits	3800	1600	3500	1200	1300	1600	1500	2000	17000/170000
Number of Beds	35	20	33	17	30	24	20	24	70
Number of potential operators	16	13	13	20	20	20	25	15	34
Personnel present at intubation									
Attending	Always	Always	Always	Always	Always	Always	Always	Sometimes	Always
PCCM fellow	Always	Always	Always	Rarely	Rarely	Rarely	Sometimes	Always	Never
Respiratory therapist	Always	Always	Always	Always	Always	Always	Always	Always	Always
Bedside nurse	Always	Always	Always	Always	Always	Always	Always	Always	Always
Charge nurse	Almost always	Sometimes	Sometimes	Always	Always	Always	Always	Almost Always	Always
Advanced Practice Provider	Sometimes	Never	Sometimes	Never	Rarely	Never	Sometimes	Sometimes	Never
Emergency Department Resident	Rarely	Never	Never	Rarely	Rarely	Rarely	Never	Sometimes	Always
Anesthesia Resident	Sometimes	Sometimes	Often	Almost always	Almost always	Almost always	Rarely	Almost Never	Never
Certified Registered Nurse Anesthetist	Never	Sometimes	Sometimes	Sometimes	Sometimes	Sometimes	Rarely	Never	Never
Airway supplies available									
Airway bag/box/cart	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
End-tidal CO_2 detector	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Tracheal tube introducer	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Laryngeal mask airways	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cricothyrotomy kit	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Direct laryngoscope	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Video laryngoscopeTypes									
McGRATH® MAC	Yes	No	No	No	No	No	No	No	No
GlideScope® GVL	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Storz C-MAC®	No	Yes	No	No	No	No	No	Yes	Yes
Monitoring									
Continuous heart rate	Always	Always	Always	Always	Always	Always	Always	Always	Always
Non-invasive blood pressure	Almost always	Always	Always	Always	Always	Always	Always	Always	Always
Invasive blood pressure	Rarely	Rarely	Rarely	Sometimes	Sometimes	Sometimes	Sometimes	Sometimes	Sometimes
Continuous oxygen saturation	Always	Always	Always	Always	Always	Always	Always	Always	Always
Bag-mask ventilation*	Randomized	Randomized	Randomized	Randomized	Randomized	Randomized	Not Randomized	Randomized	Not Randomized
Pre-medication									
Lidocaine	Rarely	Never	Never	Never	Never	Never	Never	Rarely	Never
Atropine	Never	Never	Never	Never	Never	Never	Never	Never	Never
Cricoid pressure	Rarely	Rarely	Rarely	Rarely	Rarely	Rarely	Rarely	Rarely	Sometimes
Apneic oxygenation	Sometimes	Sometimes	Sometimes	Rarely	Rarely	Rarely	Rarely	Rarely	Sometimes
Post-intubation chest radiograph	Almost always	Always	Always	Almost Always	Almost Always	Almost always	Always	Always	Always
IRB Number	161963	9296	2017.118.B	161963*	161963*	161963*	2017-050	F170608001	17-024

eTable 2. Patient Comorbidities at Baseline

Comorbidity, No. (%)	Fluid Bolus n = 168	No Fluid Bolus n = 169
COPD	34 (20%)	21 (12%)
Asthma	10 (6%)	7 (4%)
Pulmonary Embolism	4 *(2%)*	7 (4%)
Pulmonary Arterial Hypertension	3 (1%)	3 (1%)
Heart Failure	28 (16%)	25 (14%)
Coronary Artery Disease	24 (14%)	22 (13%)
Hypertension	59 (35%)	69 (40%)
Atrial Fibrillation	23 (13%)	27 (16%)
Diabetes	42 (25%)	46 (27%)
Chronic Kidney Disease	17 (10%)	22 (13%)
End-stage Renal Disease	9 (5%)	6 (3%)
Malignancy	31 (18%)	21 (12%)
Cirrhosis	21 (12%)	32 (18%)
Human Immunodeficiency Virus	3 (1%)	7 (4%)

eTable 3· Post-randomization Procedural Performance Characteristics

Characteristic	Fluid Bolus n = 168	No Fluid Bolus n = 169	*P* value	Absolute Difference (95% CI)†	Mean Difference (95% CI)†
Preoxygenation Device					
Non-rebreather Mask	50 (29·8%)	62 (36·7%)	0·21	-6·9 (-17·0 to 3·1)	
Non-invasive positive pressure	40 (23·8%)	31 (18·3%)	0·21	5·5 (-3·2 to 12·2)	
Bag Valve Mask	48 (28·6%)	36 (21·3%)	0·15	7·3 (-1·9 to 16·5)	
High Flow Nasal Cannula	27 (16·1%)	26 (15·4%)	0·86	0·7 (-7·1 to 8·5)	
Nasal Cannula	18 (11%)	21 (1·4%)	0·5	-1·7 (-8·5 to 5·1)	
Other	2 (1·2%)	5 (3·0%)	0·47	-1·8 (-4·8 to 1·3)	
Sedative Medication Used					
Etomidate	132 (78·6%)	143 (84·6%)	0·12	-6·0% (-14·3 to 2·2)	
Etomidate dose (mg/kg)	0·24 (0·20 – 0·30)	0·24 (0·20 – 0·30)	0·80		-0·00 (-0·03 to 0·02)
Fentanyl	8 (4·8%)	10 (5·9%)	0·63	-1·1 (-6·0 to 3·6)	
Fentanyl dose (mg/kg)	1·13 (0·57 – 1·74)	0·78 (0·36 – 1·29)	0·24		-0·31 (-0·89 to 0·28)
Ketamine	12 (7·1%)	9 (5·3%)	0·49	1·8 (-3·3 to 7·0)	
Ketamine dose (mg/kg)	1·48 (1·21 – 2·00)	1·63 (1·12 – 2·11)	0·67		-0·45 (-1·71 to 0·81)
Propofol	26 (15·5%)	18 (10·7%)	0·18	4·8 (-2·4 to 12·0)	
Propofol dose (mg/kg)	1·08 (0·85 - 1·58)	1·12 (0·77 - 1·51)	0·94		-0·09 (-0·63 to 0·44)
Midazolam	10 (6·0%)	12 (7·7%)	0·67	-1·7 (-7·1 to 3·6)	
Lorazepam	0	1 (0·6%)	0·15	-0·6 (-1·7 to 0·6)	
Paralytic Medication Used					
Any	156 (92·9%)	158 (93·5%)	0·98	-0·6 (-6·0 to 4·8)	
Rocuronium	92 (54·8%)	88 (52·1%)	0·54	2·7 (-8·0 to 13·3)	
Succinylcholine	65 (38·7%)	69 (40·8%)	0·68	-2·1 (-12·6 to 8·3)	
Vecuronium	1 (0·6%)	1 (0·6%)	0·99	0·0 (-1·6 to 1·6)	
Type of Laryngoscope			0·06		
Direct	98 (58·3%)	117 (69·6%)		-10·9 (-21·1 to -0·7)	
McGrath® MAC	30 (17·9%)	15 (8·9%)		9·0 (1·8 to 16·2)	
GlideScope®	22 (13·1%)	23 (13·7%)		-0·5 (-7·8 to 6·7)	
Storz C-MAC®	18 (10·7%)	12 (7·1%)		3·6 (-2·5 to 9·7)	
Fiberoptic	0 (0·0)	1 (0·6%)		-0·6 (-1·7 to 0·6)	
Training of Operator			0·45		
Pulmonary/Critical Care Fellow	130 (77·4%)	127 (75·2%)		2·2 (-6·8 to 11·3)	
Attending Physician	10 (6·0%)	14 (8·3%)		-2·2 (-7·8 to 3·2)	
Advanced Practice Provider	6 (3·6%)	8 (4·7%)		-1·2 (-5·4 to 3·1)	
Non-Anesthesia Resident	5 (3·0%)	1 (0·6%)		2·4 (-0·4 to 5·2)	
Anesthesia Resident	17 (10·1%)	18 (10·7%)		-0·5 (-7·0 to 6·0)	
Certified Registered Nurse Anesthetist	0	1 (0·6%)		-0·6 (-1·7 to 0·5)	
Number of Total Prior Intubations by Operators at the time of intubation	50 (30 - 80)	50 (30 - 100)	0·72		0·01 (-0·1 to 0·1)

Data given as median (25th percentile, 75th percentile) or number (percentage) of patients·
p-value = Mann-Whitney U Test or Chi square Test
†Differences between categorical variables
are displayed as absolute difference and

differences between continuous variables are displayed as mean differences

eTable 4. Logistic Regression Model for Cardiovascular Collapse

Characteristic	Odds Ratio of Cardiovascular Collapse	95% Confidence Interval	*P* value
Fluid Bolus	1·00	0·54 - 1·82	>0·99
Age	1·01	0·99 - 1·04	0·08
APACHE II Score	1·01	0·97 - 1·05	0·51
On Vasopressors at Enrollment	1·83	0·90 - 3·72	0·09
Lowest Systolic Blood Pressure Prior to Enrollment	0·96	0·94 - 0·98	<0·001

eTable 5. Procedural Outcomes for the Fluid Bolus vs No Fluid Bolus Groups

Procedural Outcome	Fluid Bolus (n = 168)	No Fluid Bolus (n = 169)	*P* value	Absolute Difference (95% CI)	Mean Difference (95% CI)
Number of Laryngoscopy Attempts, median (IQR)	1 (1 - 1)	1 (1 - 1)	0·66		0·0 (-0·1 to 0·1)
First Attempt Success, No· %	133 (79·2%)	138 (81·7%)	0·56	-2·4 (-11·0 to 6·0)	
Time to Intubation, median (IQR), seconds	135 (90 - 225)	131 (90 - 225)	0·95		7·0 (-20·2 to 34·3)
Best Cormack-Lehane view obtained on first attempt, No. %			0·29		
Grade I	91 (54·2%)	102 (60·4%)		-6·2 (-16·7 to 4·4)	
Grade II	41 (24·4%)	44 (26·0%)		-1·6 (-10·9 to 7·6)	
Grade III	29 (17·3%)	18 (10·7%)		6·6 (-0·8 to 14·0)	
Grade IV	7 (4·2%)	5 (3·0%)		1·2 (-2·7 to 5·2)	
Need for Second Operator, No· %	12 (7·1%)	6 (3·6%)	0·20	3·6 (-1·2 to 8·4)	

Data given as median (25^{th} percentile, 75^{th} percentile) or number (percentage) of patients·
p-value = Mann-Whitney U Test or Pearson Chi-Square Test

eTable 6. Safety Outcomes for the Fluid Bolus vs No Fluid Bolus Groups

Safety Outcome	**Fluid Bolus (n = 168)**	**No Fluid Bolus (n = 169)**	***P* value**	***Mean Difference (95% CI)***
Lowest Arterial Oxygen Saturation in 6-24 hours after intubation, median (IQR), %	95% (92 - 97)	95% (92 - 97)	·93	0·3 (-1·5 to 2·0)
Highest Fraction of Inspired Oxygen in 6-24 hours after intubation, median (IQR)	0·5 (0·4 - 0·7)	0·5 (0·4 - 0·67)	·73	-0·0 (-0·1 to 0·0)
Highest Positive End-expiratory Pressure in 6-24 hours after intubation, median (IQR), cm H2O	5 (5 - 8)	5 (5 - 8)	·36	-0·3 (-0·9 to 0·4)
Cumulative Diuretic Dose in the 24 hours after intubation, median (IQR), mg, in furosemide equivalents	0 (0 - 0)	0 (0 - 0)	·74	0·0 (-11·7 to 11·7)
Cumulative Diuretic Dose from Intubation to 72 hours after intubation, median (IQR), mg, in furosemide equivalents	0 (0 - 60)	0 (0 - 57)	·78	23·4 (-24·5 to 71·3)
Cumulative Intravenous Fluid Administration from Intubation to 72 hours after intubation, median (IQR), milliliters	2061 (955 - 4411)	2036 (628 - 4317)	·68	441 (-346 to 1229)

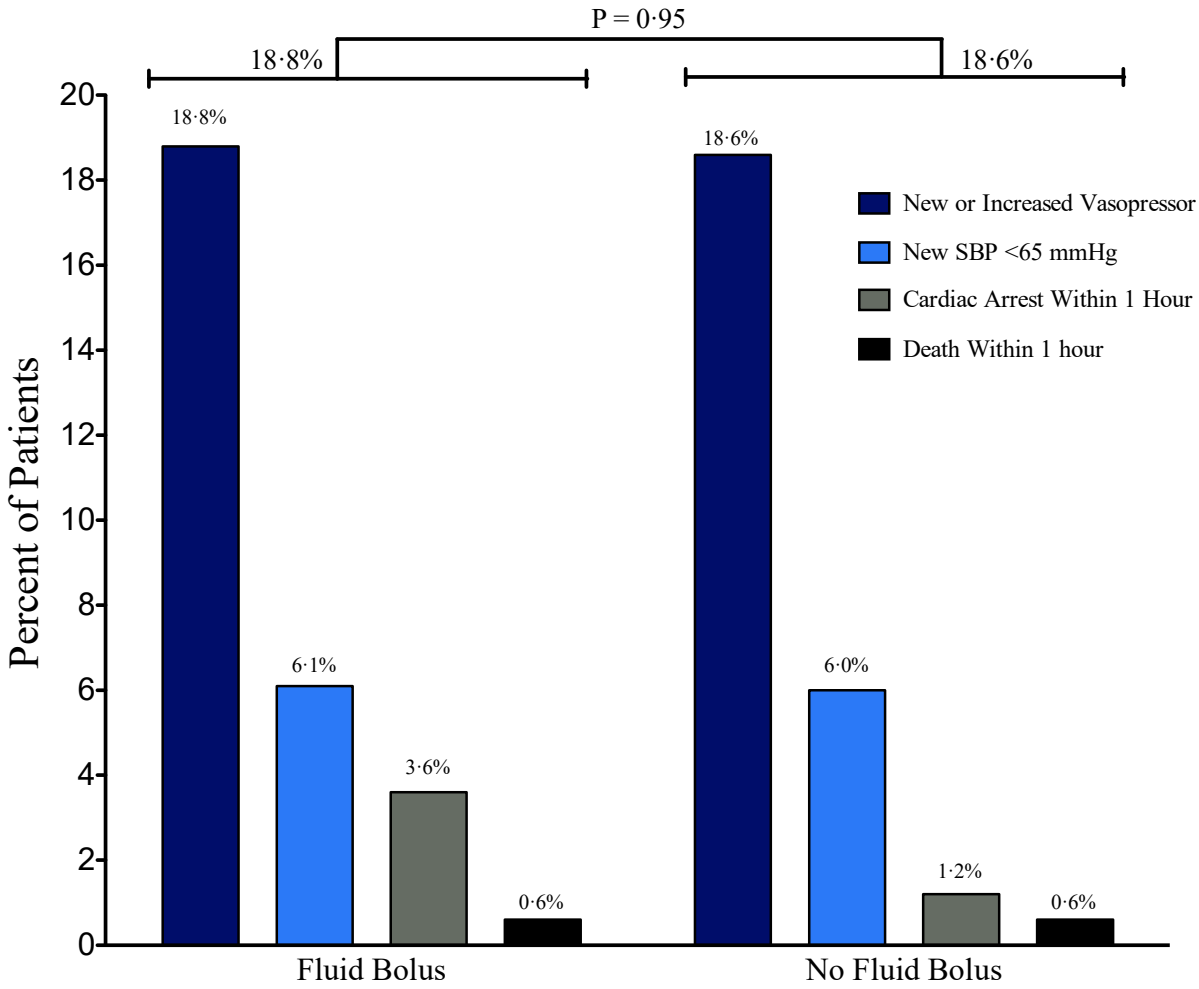
Data given as median (25^{th} percentile, 75^{th} percentile) or number (percentage) of patients.
p-value = Mann-Whitney U Test or Pearson Chi-Square Test

Table E7. Heterogeneity of Treatment Effect of Categorical Variables

		No. of Individuals		No. of Events (%)		Relative Risk Of Cardiovascular Collapse with Fluid Bolus (95% CI)	P Value for Interaction
Subgroups		Fluid Bolus	No Fluid Bolus	Fluid Bolus	No Fluid Bolus		
Co-morbidities							
Chronic Kidney Disease							
	Yes	17	22	3 (17·6)	5 (22·7)	0·77 (0·21 - 2·80)	0·59
	No	151	147	30 (19·9)	26 (17·7)	1·12 (0·69 - 1·80)	
Cirrhosis							
	Yes	21	32	3 (14·3)	2 (6·3)	2·28 (0·41 - 12·54)	0·33
	No	147	137	30 (20·4)	29 (21·2)	0·96 (0·61 - 1·51)	
Indication for Intubation							
Hypoxemic Failure							
	Yes	85	69	20 (23·5)	11 (15·9)	1·47 (0·76 - 2·86)	0·17
	No	83	100	13 (15·7)	20 (20·0)	0·78 (0·41 - 1·47)	
Hypercarbic Failure							
	Yes	16	15	4 (25·0)	5 (33·3)	0·75 (0·24 - 2·27)	0·51
	No	152	154	29 (19·1)	26 (16·9)	1·13 (0·69 - 1·82)	
Hypoxemic and Hypercarbic Failure							
	Yes	14	13	2 (14·3)	5 (38·5)	0·37 (0·08 - 1·59)	0·11
	No	154	156	31 (20·1)	26 (16·7)	1·20 (0·75 - 1·93)	
Altered Mental Status							
	Yes	47	52	9 (19·1)	11 (21·2)	0·90 (0·41 - 1·99)	0·61
	No	121	117	24 (19·8)	20 (17·1)	1·16 (0·67 - 1·98)	
Facilitate Another Procedure							
	Yes	16	25	2 (12·5)	2 (8·0)	1·56 (0·24 - 10·00)	0·66
	No	152	144	31 (20·4)	29 (20·1)	1·01 (0·64 - 1·59)	
Overall		168	169	33 (19·6)	31 (18·3)	1·07 (0·68 - 1·66)	0·76

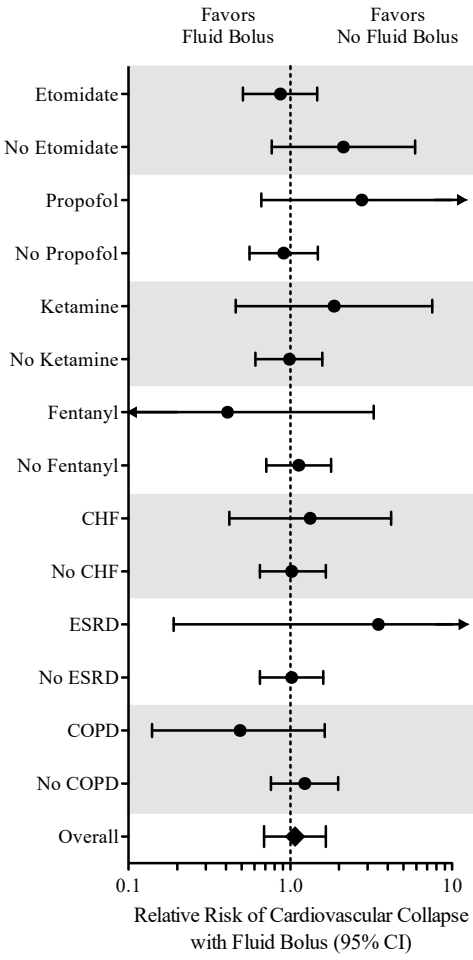
Supplemental Figures

eFigure 1. Per Protocol Analysis of the Primary Outcome



The incidence of each component of the primary outcome (y-axis) and randomization assignment (x-axis) are displayed. The horizontal bars represent the overall incidence of the primary outcome in each group. The P value represents the test for a difference between groups in the overall incidence of the primary outcome. SBP = systolic blood pressure

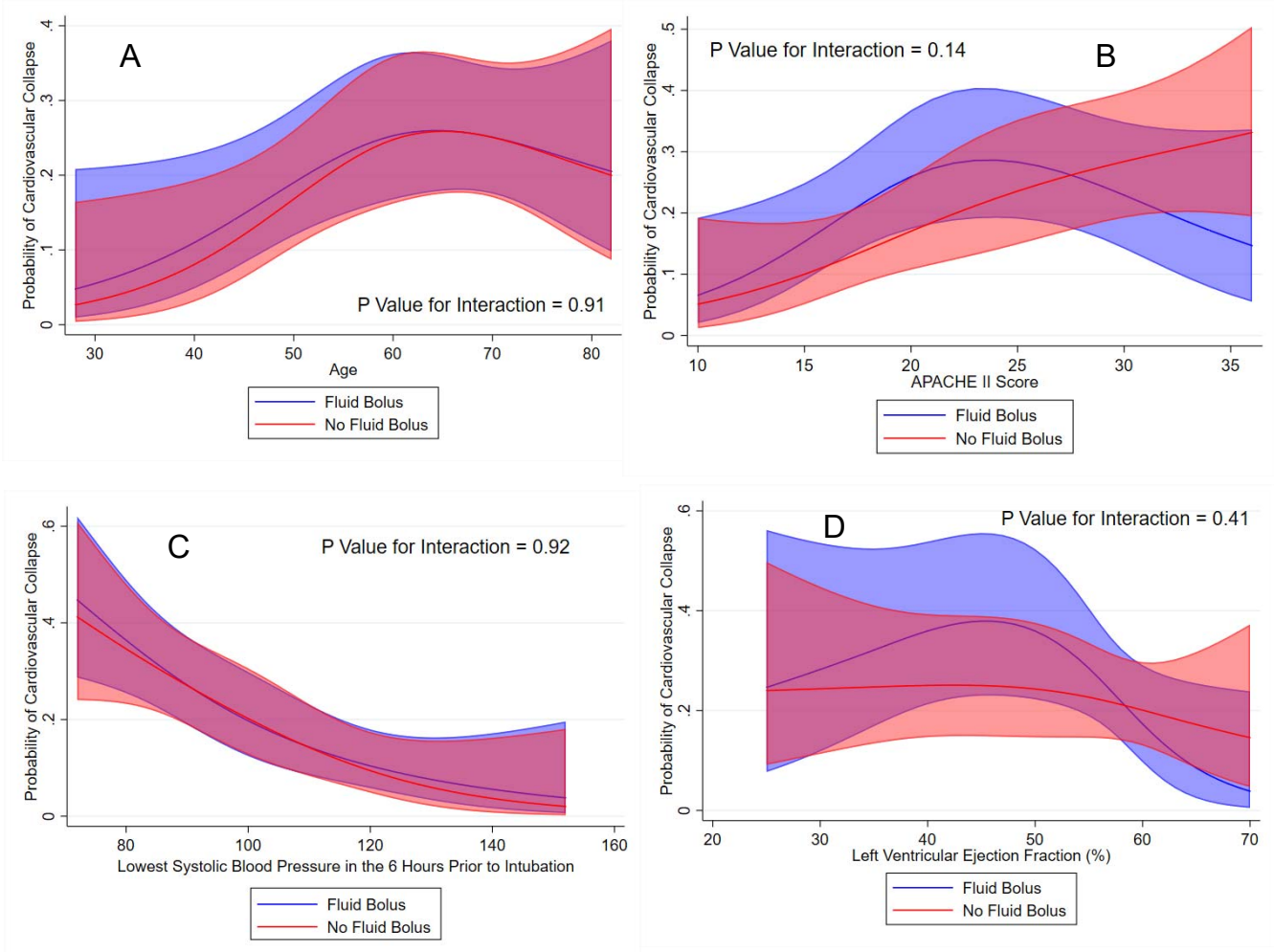
eFigure 2. Risk of Cardiovascular Collapse by Subgroup for Patients Receiving Fluid Bolus Administration vs No Fluid Bolus Administration



	No. of individuals		No. of events (%)			*P* Value for interaction
	Fluid Bolus	No Fluid Bolus	Fluid Bolus	No Fluid Bolus	RR (95% CI)	
Etomidate	130	142	21 (16·2)	27 (19)	0.87 (0.51 -1.47)	0·10
No Etomidate	38	27	12 (31·6)	4 (14·8)	2.13 (0.76 - 5.90)	
Propofol	26	18	8 (30·8)	2 (11·1)	2·76 (0·66 - 11·55)	0·13
No Propofol	142	151	25 (17.6)	29 (19·2)	0·91 (0·56 - 1·48)	
Ketamine	12	9	5 (41·7)	2 (22·2)	1·87 (0·46 -7·55)	0·37
No Ketamine	156	160	28 (17·9)	29 (18·1)	0·99 (0·61 - 1·58)	
Fentanyl	8	10	1 (12·5)	3 (30)	0·41 (0·05 - 3·28)	0·33
No Fentanyl	160	159	32 (20·0)	28 (17·6)	1.13 (0.71 - 1.79)	
CHF	28	25	6 (21·4)	4 (16·0)	1·33 (0·42 -4·20)	0·67
No CHF	140	144	27 (19·3)	27 (18·8)	1.02 (0.65 - 1.66)	
ESRD	9	6	2 (22·2)	0	3·50 (0·19 - 62·26)	0·99
No ESRD	159	163	31 (19·5)	31 (19)	1.02 (0.65 - 1.60)	
COPD	34	21	4 (11·8)	5 (23·8)	0·49 (0·14 - 1·63)	0·16
No COPD	134	148	29 (21·6)	26 (17·6)	1·23 (0·76 - 1·98)	
Overall	168	169	33 (19·6)	31 (18·3)	1·07 (0·68 - 1·66)	

The relative risk and 95% confidence interval are shown overall and according to subgroup for the percentage of patients in each study group who met the primary endpoint of cardiovascular collapse. Etomidate refers to patients who received etomidate as a procedural medication. Propofol refers to patients who received etomidate as a procedural medication. Ketamine refers to patients who received etomidate as a procedural medication. CHF refers to patients with a medical history of congestive heart failure. ESRD refers to patients with a medical history of end-stage renal disease. COPD refers to patients with a medical history of chronic obstructive pulmonary disease.

eFigure 3. Heterogeneity of Treatment Effect for Age, APACHE II Score, Systolic Blood Pressure, and Left Ventricular Ejection Fraction



Panels A-D display the probability of cardiovascular collapse obtained from logistic regression models on the Y-axis and the covariate of interest as a continuous variable on the X-axis. The P values displayed are for the interaction term between the continuous variable on the X-axis and fluid bolus randomization. Age (A), APACHE II score (B), lowest systolic blood pressure prior to enrollment (C), and previously measured left ventricular ejection fraction (D) did not significantly modify the effect of the fluid bolus on cardiovascular collapse.

Supplemental References

1. Jaber S, Jung B, Corne P, et al. An intervention to decrease complications related to tracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive Care Med*. 2010;36(2):248-255. doi:10.1007/s00134-009-1717-8.