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Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill

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At a Glance Commentary:

Scientific Knowledge on the Subject: Hypoxemia is the most common complication of emergent endotracheal intubation. Provision of supplemental oxygen by nasal cannula during laryngoscopy (apneic oxygenation) has been shown in small randomized trials to prevent desaturation during elective intubation of healthy pre-operative patients and has been recommended during intubation of the acutely ill, although it has never been tested in this setting.

What This Study Adds to the Field: This randomized clinical trial found no difference between apneic oxygenation and usual care in the lowest oxygen saturation experienced by critically ill adults undergoing emergent endotracheal intubation.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

RATIONALE: Hypoxemia is common during endotracheal intubation of critically ill patients and may predispose to cardiac arrest and death. Administration of supplemental oxygen during laryngoscopy (apneic oxygenation) may prevent hypoxemia.

OBJECTIVES: To determine if apneic oxygenation increases the lowest arterial oxygen saturation experienced by patients undergoing endotracheal intubation in the intensive care unit.

METHODS: A randomized, open-label, pragmatic trial in which 150 adults undergoing endotracheal intubation in a medical intensive care unit were randomized to receive 15 L/min of 100% oxygen via high-flow nasal cannula during laryngoscopy (apneic oxygenation) or no supplemental oxygen during laryngoscopy (usual care). The primary outcome was lowest arterial oxygen saturation between induction and two minutes after completion of endotracheal intubation.

MEASUREMENTS AND MAIN RESULTS: Median lowest arterial oxygen saturation was 92% with apneic oxygenation versus 90% with usual care (95% confidence interval for the difference -1.6% to 7.4%; *P* = .16). There was no difference between apneic oxygenation and usual care in incidence of oxygen saturation < 90% (44.7% versus 47.2%; *P* = .87), oxygen saturation < 80% (15.8% versus 25.0%; *P* = .22), or decrease in oxygen saturation > 3% (53.9% versus 55.6%; *P* = .87). Duration of mechanical ventilation, intensive care unit length of stay, and in-hospital mortality were similar between study groups.

CONCLUSIONS: Apneic oxygenation does not appear to increase lowest arterial oxygen saturation during endotracheal intubation of critically ill patients compared to usual care.

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These findings do not support routine use of apneic oxygenation during endotracheal intubation of critically ill adults.

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INTRODUCTION

Hypoxemia is the most common complication of endotracheal intubation in the critically ill[1–4] and the strongest risk factor for peri-procedural cardiac arrest and death[5]. The traditional approach to avoiding desaturation during intubation is pre-oxygenation[6–10]. However, in critically ill patients, acute physiologic abnormalities render pre-oxygenation less effective[7] and often insufficient to prevent desaturation during even short periods of apnea[11].

Apneic oxygenation is the delivery of supplemental oxygen to the nasopharynx in the absence of ventilation[12]. Even without lung expansion, alveolar oxygen diffuses into the bloodstream and is consumed into carbon dioxide. Because of carbon dioxide's high affinity for hemoglobin and effective buffering, the volume of carbon dioxide returned to the alveoli is less than the volume of oxygen removed. As a result, alveolar pressure decreases and gas is drawn down from the nasopharynx[10]. By increasing the fraction of oxygen in the gas moving from the nasopharynx to the lungs, apneic oxygenation aims to prevent arterial desaturation.

Apneic oxygenation has been used to prevent desaturation in patients undergoing brain death examination[13], bronchoscopy[14], endoscopy[15], and even elective endotracheal intubation for general anesthesia[16–19]. Although administration of oxygen by nasal cannula[20] during laryngoscopy has been adopted in many emergency departments[21] and intensive care units (ICU)[22], there are significant differences between intubating electively in the operating room and urgently in out-of-operating room settings. Despite two recent "before-after" studies suggesting benefit for apneic oxygenation in out-of-operating room intubations[22,23], the effectiveness of apneic oxygenation in this context remains unclear. We conducted a prospective, randomized trial comparing the impact of apneic oxygenation versus usual care on

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lowest arterial oxygen saturation during endotracheal intubation of critically ill adults. We hypothesized that the lowest arterial oxygen saturation during intubation would be higher with apneic oxygenation.

METHODS

Study Design

The FELLOW (Facilitating EndotracheaL intubation by Laryngoscopy technique and apneic Oxygenation Within the intensive care unit) Study was a randomized, open-label, parallel-group, pragmatic trial comparing apneic oxygenation to usual care during endotracheal intubation of critically ill adults. The trial was factorialized to also compare direct versus video laryngoscopy, the details of which will be reported separately. The study protocol was approved by the institutional review board at Vanderbilt University with waiver of informed consent. The trial was registered online prior to initiation (NCT02051816) and the statistical analysis plan was made publically available prior to completion of enrollment (https://starbrite.vanderbilt.edu/rocket/page/FELLOW; available in the online data supplement).

Study Participants

From February 13, 2014 to February 11, 2015 we enrolled patients undergoing endotracheal intubation in the medical ICU at Vanderbilt University Medical Center. All patients 18 years or older being intubated by a pulmonary and critical care medicine fellow were eligible. Patients were excluded if awake intubation was planned, if intubation was

required so emergently that randomization could not be achieved, or if the treating clinicians felt a specific approach to intra-procedural oxygenation or a specific laryngoscopy device was mandated for the safe performance of the procedure (Figure 1).

Randomization

Eligible patients were randomly assigned in a 1:1 ratio to receive apneic oxygenation (intervention) or usual care (control). Per the factorial design, patients were also simultaneously randomized to either video or direct laryngoscopy – details of which will be reported separately. The sequence of study group assignments was generated via a computerized algorithm using permuted blocks of 4, 8, and 12. Study group assignments were placed in sequentially-numbered opaque envelopes which remained sealed until the decision had been made that a patient required intubation and was enrolled in the study.

Study Treatments

For all patients, study protocol governed only provision of supplemental oxygen during apnea and laryngoscopy device used on the first laryngoscopy attempt. Decisions regarding intubation, approach to pre-oxygenation, patient positioning, medications for induction and neuromuscular blockade, ventilation between induction and laryngoscopy, choice of laryngoscope blade type and size, and use of additional airway management equipment were made by the clinical team. Intubation practices in the study environment are detailed in the online data supplement. Operator compliance with general best-practices in airway

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management was prospectively collected from a convenience sample of consecutive intubations.

Although pre-oxygenation was allowed, patients in the usual care group were intubated without supplemental oxygen during laryngoscopy. For patients in the apneic oxygenation group, a high-flow nasal cannula (Comfort Soft Plus™; Westmed, Inc., Arizona, USA) set to 15 L/min flow of 100% oxygen was placed in the patient's nares prior to induction and kept in place until intubation was complete. Because of the nature of the study intervention, clinicians and study personnel were aware of study group assignments after enrollment.

Data Collection

To minimize observer bias, data collection during intubation was performed by independent observers unaware of the study hypothesis and not involved in the performance of the procedure. To confirm the accuracy of data collected by the independent observers, the primary investigators concurrently assessed the same outcomes for a convenience sample of around 10% of study intubations.

Subjective assessments of Cormack-Lehane grade of view[24], difficulty of intubation, and airway complications during the procedure were self-reported by the operator. All other data on baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes were collected from the medical record by study personnel. All patients were followed until the first of hospital discharge, death, or 28 days after enrollment.

Study Outcomes

The primary outcome was the lowest arterial oxygen saturation measured by continuous pulse oximetry (SpO_2) between induction and two minutes after successful endotracheal tube placement ("lowest arterial oxygen saturation"). Secondary efficacy outcomes included incidence of hypoxemia ($SpO_2 < 90\%$), severe hypoxemia ($SpO_2 < 80\%$), desaturation (decrease in SpO_2 greater than 3%), and change in saturation from baseline. Secondary safety outcomes included Cormack-Lehane grade of glottic view[24], incidence of successful intubation on the first laryngoscopy attempt (placement of an endotracheal tube in the trachea during the first insertion of the laryngoscope into the oral cavity without the use of any other devices), number of laryngoscopy attempts, time from induction to intubation, need for additional airway equipment or operators, and incidence of non-hypoxemia complications. Tertiary outcomes included duration of mechanical ventilation, ICU length of stay, and in-hospital mortality.

Statistical Analysis

Anticipating a standard deviation of 10 percent in lowest arterial oxygen saturation[6], enrollment of 150 patients would provide 80 percent statistical power (at a two-sided alpha level of 0.05) to detect a difference between groups in mean lowest arterial oxygen saturation of 4.6 percent – within the 5 percent minimum difference considered clinically meaningful in prior studies[6,9,17,18,22] (details available in the online data supplement).

Analyses were conducted according to a statistical analysis plan that was publically available prior to completion of enrollment. Continuous variables were reported as mean ± standard deviation or median and interquartile range; categorical variables as frequencies and

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proportions. Between-group differences were analyzed with the Mann-Whitney rank sum test for continuous variables, Fisher exact test for categorical variables, and Spearman rank correlation coefficient for correlation between two continuous variables.

The primary analysis was an unadjusted, intention-to-treat comparison of patients randomized to apneic oxygenation versus usual care with regard to the primary outcome of lowest arterial oxygen saturation.

We performed four pre-specified secondary analyses: (1) The effect of the intervention on secondary and tertiary outcomes, (2) The effect of the intervention on the primary outcome in pre-specified patient and procedural subgroups, (3) "Per-protocol" analyses comparing lowest arterial oxygen saturation between patients who received apneic oxygenation and those who did not, and (4) Linear regression for the outcome of lowest arterial oxygen saturation in which the exposure variable of randomized group assignment was accompanied first by just the covariate of oxygen saturation at induction and then by potential baseline confounders. Subgroup analyses were performed using logistic regression with heterogeneity of treatment effect determined on the basis of statistical test for interaction between treatment assignment and subgrouping variable. A two-sided P value < 0.05 was used to determine significance. All analyses were performed using SPSS Statistics v.22 (IBM Corp., Armonk, NY, USA) or R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Enrollment and Baseline Characteristics

Of 196 medical ICU patients intubated by fellows during the study period, 150 met no

exclusion criteria and were enrolled (Figure 1). Patients randomized to receive apneic oxygenation (n = 77) and usual care (n = 73) were similar at baseline (Table 1). There was no difference between the two arms in the prior airway management experience of the fellow performing the intubation (Table 1). There were no differences in method of pre-oxygenation (Table 1), choice of induction agent or neuromuscular blocker, ventilation between induction and laryngoscopy, or laryngoscope type, except for higher propofol use for induction in the usual care arm (13.7% versus 2.5%; *P* = .02) (Table E1 in the online data supplement). Oxygen saturation at the time of induction was 99% [IQR 96-100%] with apneic oxygenation compared to 98% [IQR 94-99%] with usual care (*P* = .03).

Airway Management

Five patients (6.8%) in the usual care arm received apneic oxygenation during intubation and two patients (2.6%) in the apneic oxygenation arm did not (Figure 1). There was no difference between those randomized to apneic oxygenation and usual care in the rate of successful intubation on the first laryngoscopy attempt (67.5% versus 67.1%; *P* = .96), time from induction to secured airway (150 seconds versus 132 seconds; *P* = .31), or any other recorded aspect of the performance of the procedure (Table 2; Table E2 in the online data supplement).

Main Outcomes

There was no significant difference between apneic oxygenation and usual care with regard to the primary outcome of median lowest arterial oxygen saturation during the

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procedure: 92% [IQR 84-99%] versus 90% [IQR 80-96%] respectively (*P* = .16) (Figure 2). Apneic oxygenation did not impact the proportion of patients who experienced an oxygen saturation less than 90%, less than 80%, or a desaturation greater than 3% during the procedure (Table 2). There were no differences in duration of mechanical ventilation, ICU length of stay, or in-hospital mortality (Table 2).

In multivariable linear regression adjusting for saturation at induction alone or with age, body mass index, APACHE II score, shock, prior noninvasive ventilation, highest fraction of inspired oxygen in the prior six hours, laryngoscope choice, and operator experience, apneic oxygenation did not impact the lowest arterial oxygen saturation during the procedure (Table E3 in the online data supplement).

Secondary Analyses

There was no difference in lowest arterial oxygen saturation between apneic oxygenation and usual care in any of the subgroups examined (Figure 3). Specifically, apneic oxygenation was not significantly more effective for patients at potentially greater risk for hypoxemia based on higher FiO_2 requirement, lower oxygen saturation at induction, lower ratio of oxygen saturation to FiO_2 ($SpO2/FiO_2$ ratio[25]) in the prior six hours, higher body mass index, more difficult intubation, or longer duration of laryngoscopy (Figure E1 in the online data supplement). The type of laryngoscopy device assigned did not modify the effect of apneic oxygenation on lowest arterial oxygen saturation (*P* value for the interaction = .15, Figure E2 in the online data supplement).

One patient in each arm of the study was missing a value for lowest arterial oxygen

saturation. In sensitivity analyses imputing both values (by carrying forward the saturation at induction or by assigning apneic oxygenation the highest possible saturation and usual care the lowest), there remained no difference between apneic oxygenation and usual care.

In an *a priori* defined per-protocol analysis comparing patients who received apneic oxygenation (n=80) to those who did not (n=68), there was no difference in lowest arterial oxygen saturation (92% [IQR 84-98%] versus 90% [IQR 80-96%] respectively; *P* = .21) or in any other clinical outcome (Table E4, Table E5, and Figure E3 in the online data supplement).

The values for lowest arterial oxygen saturation recorded concurrently by independent observers and the primary investigators were strongly correlated (Spearmen's R^2 = 0.893; *P* <0.001). Operators were frequently compliant with general best-practices in airway management including pre-oxygenation, equipment preparation, end-tidal carbon dioxide detector availability, and presence of a second operator (Table E6 in the online data supplement).

DISCUSSION

This randomized trial comparing apneic oxygenation to usual care during endotracheal intubation of critically ill adults found that apneic oxygenation did not increase the lowest arterial oxygen saturation. There were no significant differences between apneic oxygenation and usual care in any primary or secondary outcome, overall or in any subgroup.

Hypoxemia is the most common complication of endotracheal intubation[1–3] and the most closely linked to cardiac arrest and death[5]. Pre-oxygenation is often insufficient to prevent desaturation during intubation[3,11] and the provision of supplemental oxygen during

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apnea has been advocated as a safe and inexpensive intervention to improve peri-intubation oxygenation[10,26,27]. The utility of apneic oxygenation has been reported in four small randomized trials in the operating room[16–19] and two "before-after" studies of emergent intubation[22,23]. Trials of apneic oxygenation during elective anesthesia ranged in size from 12 to 34 patients, all without acute pulmonary dysfunction[16–19]. Provision of 3-5L/min of oxygen nasally significantly prolonged the duration of apnea without desaturation[16–19]. Outside the operating room, Miguel-Montanes et al observed higher oxygen saturation during intubation after their ICU switched from apneic oxygenation at 6 L/min to 60 L/min[22] and Wimalasena et al reported a 6% decrease in the incidence of desaturation after their helicopter emergency medical service adopted apneic oxygenation at 15 L/min by nasal cannula[23].

In contrast to prior studies, our trial showed no difference between apneic oxygenation and usual care. There are several potential explanations for this discordance. Prior reports of apneic oxygenation's utility outside the operating room were "before-after" designs in which other changes over time may have confounded the perceived impact of apneic oxygenation. Self-reported outcomes in prior studies may have predisposed to observer bias. In contrast to healthy patients undergoing elective anesthesia[16–19] and patients intubated primarily for traumatic, hemodynamic, or neurologic conditions[22,23], most patients in our study were intubated for respiratory failure. For patients with pulmonary function so abnormal that provision of oxygen by mask or non-invasive ventilation was insufficient to avert intubation, providing 15 L/min by nasal cannula during intubation might be expected to be similarly ineffective. Although our analyses did not suggest efficacy for apneic oxygenation in any subgroup, whether apneic oxygenation could be effective in patients with normal pulmonary

function being intubated for other reasons requires further study. Finally, whether the 'dose' of apneic oxygenation delivered was adequate is important. Our use of 15 L/min via high-flow nasal cannula was based on expert recommendation[10] and is a higher flow rate than prior trials in the operating room[16–19] but lower than the 60 L/min delivered in a recent observational study[22]. It seems unlikely that a higher flow rate would improve results, however, based on the recent PREOXYFLOW trial[9]. Although the PREOXYFLOW trial focused on pre-oxygenation with high-flow nasal cannula versus face mask, saturation at induction was the same in both arms and the high-flow nasal cannula continued to deliver 60 L/min of oxygen during laryngoscopy compared to no oxygen delivery in the control arm. Median lowest arterial oxygen saturations for those receiving 60 L/min apneic oxygenation versus none were identical to our study at 92% and 90%, respectively.

Our study has several strengths. It is the first randomized trial specifically comparing apneic oxygenation to usual care during intubations outside the operating room and is five times larger than any prior trial. The primary outcome, lowest arterial oxygen saturation during intubation, is of interest to clinicians, has been used in prior airway management trials, and is linked to patient-centered outcomes like cardiac arrest and death. Collection of study endpoints by an independent observer and contemporaneous validation of these data by the primary investigators reduces potential for observer bias. The limited exclusion criteria and relatively small number excluded promote generalizability.

Our study also has limitations. Conduct in one medical ICU at a single academic center may limit generalizability. High compliance with pre-oxygenation (including non-invasive ventilation for patients with hypoxemia), patient positioning, and equipment preparation best-

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practices may have reduced the potential additive impact of apneic oxygenation[6,28,29]. Had we used a standardized intubation protocol[6] or a highly-uniform group of operators[7], we might have reduced practice-related variation in lowest arterial oxygen saturation, making any effect of apneic oxygenation easier to detect. Comparing apneic oxygenation to a nasal cannula delivering ambient air ('placebo') could have allowed blinding -- but would have inaccurately represented usual care, obscured complications related to the delivery of the intervention (e.g. disruption of mask seal for bag-valve-mask ventilation by the nasal cannula itself), and created a safety hazard by providing a false source of oxygen to teams conducting emergent intubation. Our study was powered to detect the 5% difference in lowest arterial oxygen saturation that has been considered clinically meaningful in prior trials[6,9,17,18], but a smaller difference might have been missed. Exclusion of patients clinically determined to require video laryngoscopy may limit applicability of our results to patients with abnormal upper airway anatomy at risk for prolonged intubation times. Although not observed in our analyses, benefit in specific subgroups of patients (e.g. severe hypoxic respiratory failure, preserved pulmonary function) cannot be excluded.

The results of our trial suggest that, for patients being intubated in the medical ICU, routine use of apneic oxygenation is safe but ineffective. Safety without efficacy is insufficient in the high-stakes, time-sensitive world of emergent endotracheal intubation and clinicians should focus their resources on interventions that prevent complications (e.g. effective pre-oxygenation[6]). Future research should employ rigorously designed trials either to identify populations who do benefit from apneic oxygenation or shift focus to other aspects of airway management with potential to improve patient outcomes.

In summary, the results of this clinical trial suggest that apneic oxygenation during endotracheal intubation of critically ill adults does not increase lowest arterial oxygen saturation compared to usual care. Routine use of apneic oxygenation during emergent intubation cannot be recommended.

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FIGURE LEGENDS

Figure 1. Enrollment, randomization, intervention, and analysis. Of 196 adults intubated by pulmonary and critical care medicine fellows during the study period, 46 were excluded and 150 were randomized, followed, and included in the intention-to-treat analysis.

Figure 2. Lowest arterial oxygen saturation by study group. (A) The primary outcome of lowest arterial oxygen saturation between induction and two minutes after completion of endotracheal intubation (lowest oxygen saturation) is displayed for patients randomized to apneic oxygenation (squares) and usual care (circles). Horizontal bars represent median and interquartile range. (B) The relationship between oxygen saturation at induction and lowest oxygen saturation is displayed for each patient in the usual care (left) and apneic oxygenation (right) groups.

Figure 3. Subgroup Analyses. The mean difference in lowest arterial oxygen saturation (%) between apneic oxygenation and usual care is given for patients in pre-specified subgroups present at the time of induction (black circles) and arising after procedure initiation (grey squares). Vertical bars represent the 95% confidence interval around the mean difference. FiO_2 in 6h prior is the highest fraction of inspired oxygen in the 6 hours prior to the intubation; BMI is body mass index in kg/m^2; time to intubation is the time from induction until successful endotracheal intubation.

TABLES

Table 1. Patient and operator characteristics at baseline.

	Usual Care	Apneic Oxygenation
Patient Characteristics	**(n = 73)**	**(n = 77)**
Age, median [IQR], years	60 [50-67]	60 [51-68]
Men, No. (%)	46 (63.0%)	45 (58.4%)
Caucasian, No. (%)	62 (84.9%)	63 (82.9%)
Body Mass Index, median [IQR], kg/m2	28.6 [23.4-32.8]	28.6 [23.3-32.8]
APACHE II score, median [IQR]	22 [17-27]	22 [16-27]
Vasopressors, No. (%)	9 (12.3%)	11 (14.3%)
Lowest MAP in prior 6 hours, median [IQR], mm Hg	68 [57-80]	65 [57-79]
Lowest oxygen saturation in prior 6 hours, median [IQR], %	91 [88-93]	92 [88-95]
Highest FiO2 in prior 6 hours, median [IQR]	0.40 [0.30-0.80]	0.40 [0.27-0.60]
BiPAP use in prior 6 hours, No. (%)	31 (42.5%)	26 (33.5%)
Re-intubation within 24 hours of extubation, No. (%)	11 (15.1%)	9 (11.7%)
Intensive care unit diagnoses, No. (%)		
Sepsis	50 (68.5%)	49 (63.6%)
Septic Shock	14 (19.2%)	20 (26.0%)
Hemorrhagic Shock	3 (4.1%)	6 (7.8%)
Cardiogenic Shock	1 (1.4%)	2 (2.6%)
Myocardial Infarction	9 (12.3%)	4 (5.2%)
COPD Exacerbation	8 (11.0%)	4 (5.2%)
Hepatic Encephalopathy	10 (13.7%)	10 (13.0%)
Delirium	35 (50.0%)	33 (43.4%)
Indication for Intubation, No. (%)		
Hypoxic or hypercarbic respiratory failure	42 (57.5%)	43 (55.8%)
Altered mental status or encephalopathy	18 (24.7%)	21 (27.3%)
Other	13 (17.8%)	13 (16.8%)
Co-morbidities complicating intubation, No. (%)		
BMI > 30 kg/m2	23 (31.5%)	25 (32.5%)
Upper Gastrointestinal Bleeding	7 (9.6%)	6 (7.8%)
Limited Mouth Opening*	3 (4.1%)	3 (3.9%)
Limited Neck Mobility*	3 (4.1%)	2 (2.6%)
Head or Neck Radiation	1 (1.4%)	0 (0.0%)
Airway Mass or Infection	0 (0.0%)	1 (1.3%)
Witnessed Aspiration	1 (1.4%)	0 (0.0%)
Epistaxis or oral bleeding	0 (0.0%)	0 (0.0%)

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Pre-oxygenation†, No. (%)		
Non-rebreather mask	32 (43.8%)	25 (32.5%)
BiPAP	23 (31.5%)	23 (29.9%)
Bag-valve-mask ventilation‡	31 (42.5%)	33 (42.9%)
Standard nasal cannula§	2 (2.7%)	6 (7.8%)
Other	1 (1.4%)	0 (0.0%)
Oxygen saturation at induction, median [IQR], %	98 [94-99]	99 [96-100]
Operator Characteristics		
Total number of prior intubations, median [IQR]	56 [40-69]	68 [52-69]
Months of fellowship training, median [IQR]	21.5 [14.4 - 29.5]	22.9 [15.4-31.6]

Data are presented as median [25th percentile – 75th percentile] or number (percentage).

APACHE II is Acute Physiology and Chronic Health Evaluation II – ranging from 0 to 71 with higher scores indicating higher severity of illness; MAP is mean arterial pressure; FiO_2 is fraction of inspired oxygen; BiPAP is Bilevel Positive Airway Pressure; Shock is mean arterial pressure less than 65 mm Hg or vasopressor use; COPD is chronic obstructive pulmonary disease; BMI is body mass index. Non-invasively measured oxygen saturation (SpO2) at the time of induction was higher in the apneic oxygenation arm (P = 0.03).

*As reported by the fellow performing the intubation.

†Patients could receive more than one method of pre-oxygenation.

‡Bag-valve-mask ventilation was routinely accompanied by use of a positive end-expiratory pressure valve set to 5-10 cmH_20.

§Standard nasal cannula delivered less than 6 L/min of non-humidified oxygen.

Table 2. Study Outcomes.

	Usual Care	Apneic Oxygenation	
Oxygenation Outcomes	**(n = 73)**	**(n = 77)**	***P* Value**
Lowest oxygen saturation, median [IQR], %	90 [80-96]	92 [84-99]	.16
Lowest oxygen saturation < 90%, No. (%)	34 (47.2%)	34 (44.7%)	.87
Lowest oxygen saturation < 80%*, No. (%)	18 (25.0%)	12 (15.8%)	.22
Decrease in oxygen saturation, median [IQR], %	4.5 [1-14]	4.0 [0-12]	.60
Decrease in oxygen saturation > 3%, No. (%)	40 (55.6%)	41 (53.9%)	.87
Procedural Outcomes			
Intubation on the first laryngoscopy attempt, No. (%)	49 (67.1%)	52 (67.5%)	.96
Number of laryngoscopy attempts, median [IQR]	1 [1-2]	1 [1-1]	.60
Time from induction to secured airway, median [IQR], seconds	150 [102-245]	132 [88-205]	.31
Clinical Outcomes			
Duration of mechanical ventilation, median [IQR], days	3 [2-7]	3 [1-10]	.73
Intensive care unit length of stay, median [IQR], days	7 [3-10]	4 [2-9]	.24
Died within one hour of intubation, No. (%)	1 (2.8%)	0 (0.0%)	>.99
Died before hospital discharge, No. (%)	36 (49.3%)	27 (35.1%)	.10

Data are presented as median [25th percentile – 75th percentile] or number (percentage). There were no differences between the study groups in the primary outcome of lowest arterial oxygen saturation between induction and two minutes after completion of the procedure, secondary procedural outcomes, or clinical outcomes.

*Lowest oxygen saturation < 80% was added to the analysis *post hoc*.

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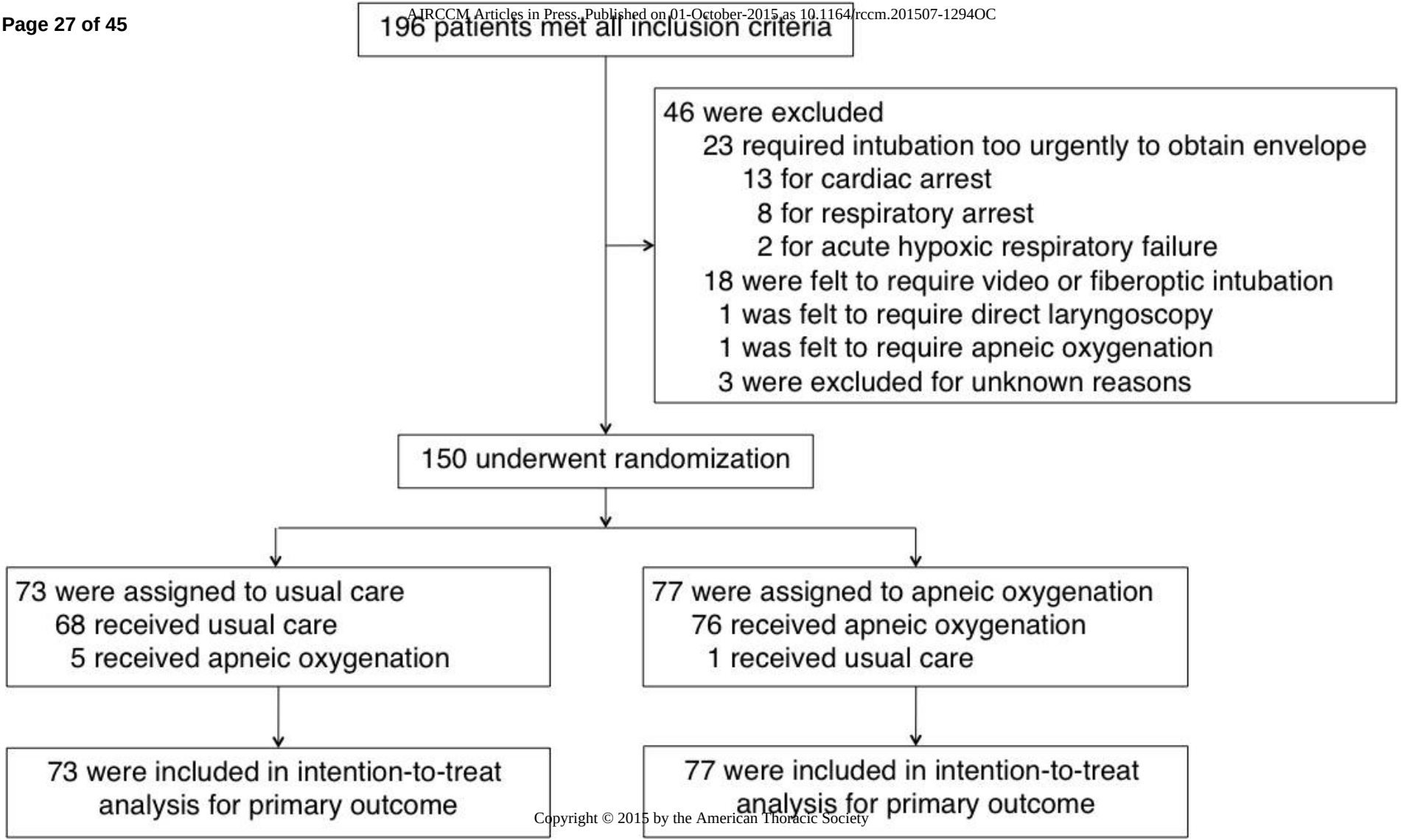

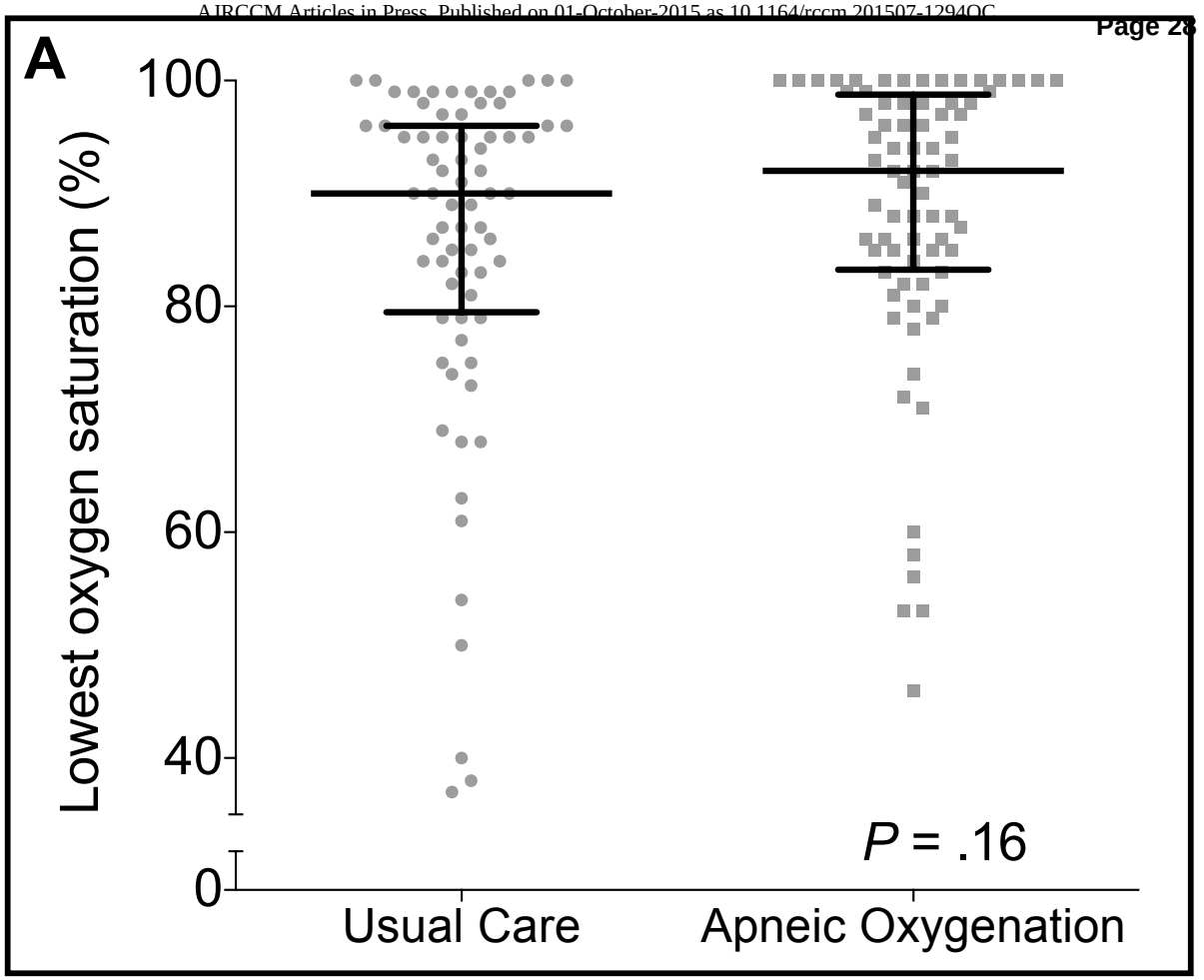

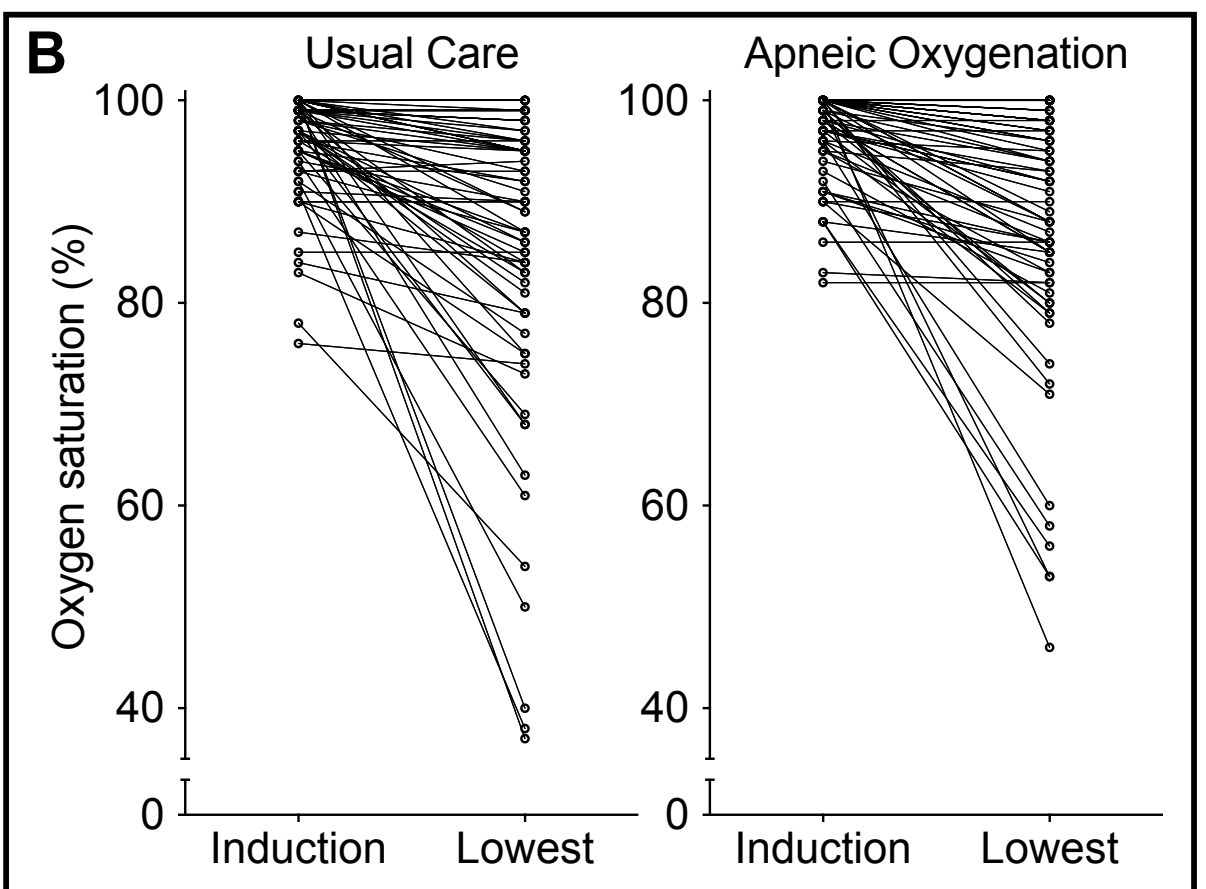

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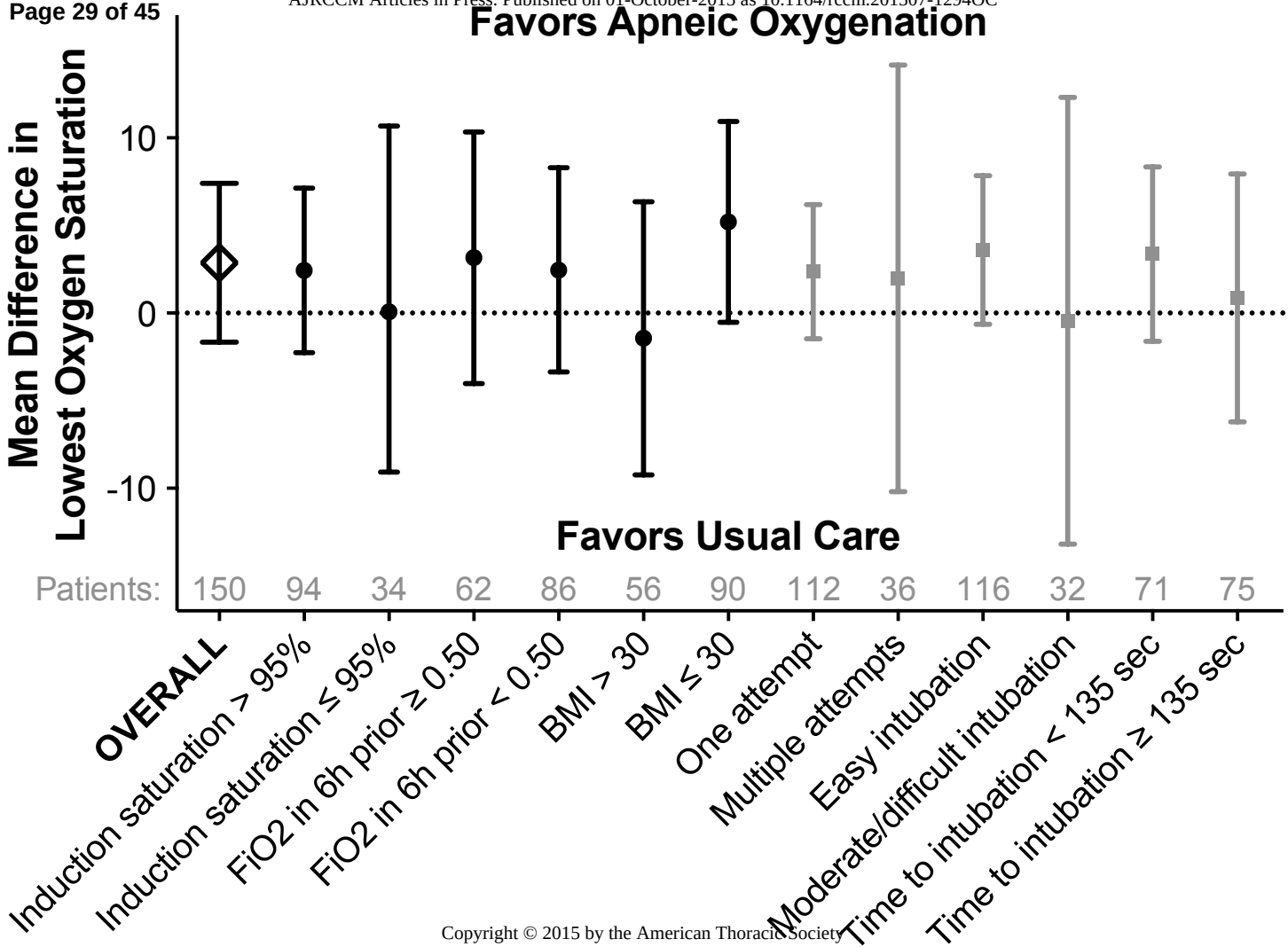

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Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill

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Online Data Supplement

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SUPPLEMENTAL METHODS

A. Intubation Practices in the Study Environment

The medical intensive care unit (ICU) at Vanderbilt University Medical Center is a 34-bed unit with over 3,700 admissions annually. Each patient is cared for by an attending physician board-certified in Pulmonary and Critical Care Medicine (PCCM), a clinical fellow training in PCCM, and a team of internal medicine, emergency medicine, and anesthesia housestaff or acute care nurse practitioners. When a patient on the unit requires endotracheal intubation, personnel present include a PCCM attending (98% of intubations in this study) or Anesthesia attending (2% of intubations in this study), the PCCM fellow performing the procedure (100% of intubations in this study), a bedside nurse to administer medications (100% of intubations in this study), a respiratory therapist (91% of intubations in this study), a 'charge' nurse or 'help-all' nurse (100% of intubations in this study), and available housestaff or nurse practitioners from the patient's care team.

Pre-oxygenation is initiated by the nurse or respiratory therapist with supervision from the fellow. The approach to pre-oxygenation varies with the circumstances of and indication for intubation. Patients with severe impairments in oxygenation, ventilation, hemodynamics, or mental status frequently receive bag-valve-mask ventilation (BVM) with a positive end-expiratory pressure valve set to 5-10 cmH_2O for pre-oxygenation (43% of all intubations in this study). Among patients stable enough to tolerate other approaches to pre-oxygenation, bilevel positive airway pressure (BiPAP) is employed more frequently for patients with hypoxic respiratory failure (66% of patients with an $FiO2 \geq 0.4$ compared to 7% of patients with an $FiO2 < 0.4$ in this study). Patients who are not pre-oxygenated with BVM ventilation or BIPAP (only 30% of all intubations in this study) receive a non-rebreather mask with 15L/min flow of 100% oxygen (64% of those without BIPAP or BVM in this study), standard nasal cannula (11% of those without BIPAP or BVM in this study), or other approaches such as high-flow nasal cannula (25% of those without BIPAP or BVM in this study). When the patient's clinical status allows, pre-oxygenation is continued for at least three minutes with a goal noninvasive oxygen saturation of 100%.

With pre-oxygenation ongoing, one of four "airway bags" stationed around the unit containing direct laryngoscopes with a variety of blade types and sizes, stylets and endotracheal tubes ranging from size 5.0 to 9.0, endotracheal tube introducers, end-tidal carbon dioxide detectors, laryngeal mask airways, surgical lubricant, a cricothyrotomy kit, and other adjunctive airway supplies is brought to the fellow at the head of the bed. A McGRATH® MAC Video Laryngoscope, GlideScope® video laryngoscope, or Olympus® BF-P180 bronchovideoscope are available on the unit. With the help of the respiratory therapist, the fellow sets up and tests the suction, laryngoscope and blade, endotracheal tube and stylet. An in-room computer is frequently employed to review the patient's prior airway management records and clinical and laboratory data as an induction agent, neuromuscular blocker, and ancillary treatments such as phenylephrine, intravenous fluid boluses, and post-intubation sedation are ordered. Noninvasive continuous monitoring of heart rate and oxygen saturation are coupled with frequent cycling (2 or 3 minute intervals) of noninvasive blood pressure monitoring.

Patient positioning occurs either at the start of pre-oxygenation or at the time of induction (for agitated patients or those requiring upright position for severe dyspnea). The attending and fellow jointly determine the best position based on the patient and illness characteristics. The most commonly employed position is the 'sniffing' position with the bed flat and the patient's head elevated by towels or blankets, however ramping of the patients shoulders with towels or blankets, elevation of the head-of-bed to 20-30 degrees, or intubation with the patient completely flat may also be elected.

When set-up is complete, the fellow asks for the administration of an induction agent followed immediately by a neuromuscular blocker and a saline flush. Rapid sequence intubation with use of neuromuscular blockade is standard (97% of intubations in this study). Pre-medication with lidocaine or atropine is rare. Phenylephrine is frequently available but not administered until indicated. For patients who are already receiving a fluid bolus, the bolus is continued. For patients who are not actively receiving a fluid bolus, a one liter bag of isotonic crystalloid is made available. The decision regarding prophylactic versus 'as needed' fluid bolus administration is made by the clinical team weighing the potential hemodynamic benefits against

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the potential short- and long-term risks of additional fluid receipt.

After achievement of neuromuscular blockade, the fellow advances the laryngoscope blade without cricoid pressure unless requested to assist with laryngeal visualization. After adjusting position, suctioning, or bimanual manipulation as needed to optimize view of the glottis, the fellow is handed the endotracheal tube or endotracheal tube introducer to secure the airway. In cases in which the fellow is unable to successfully pass an endotracheal tube on the first or second attempt, the attending physician frequently takes over management of the airway (6% of intubations in this study). In the event that the attending physician is unable to intubate the patient, an overhead stat call is placed for the anesthesia airway team to attempt the intubation (< 1% of intubations in this study). In the event that the anesthesia airway team is unable to complete the intubation, an attending trauma surgeon is available in the hospital 24/7 to perform emergent cricothyrotomy (0% of intubations in this study).

Once an endotracheal tube is successfully passed, the balloon is inflated and end-tidal carbon dioxide detector placed by the respiratory therapist. The attending physician and one other provider auscultate for bilateral breath sounds. The endotracheal tube depth is adjusted if needed and the tube is secured in place by the respiratory therapist. All patients are placed by the respiratory therapist on a protocol for ventilation with low tidal volumes (6cc/kg predicted body weight) using a volume control mode of ventilation. Intermittent or continuous infusion analgesia or sedation are commonly ordered prior to initiation of the procedure and started after post-procedure vital signs demonstrate stability. Endotracheal tube placement is then confirmed by a chest radiograph (94% of intubations in this study).

B. Power Calculation

In the absence of prior data within our study population, we felt the randomized trial of non-invasive ventilation for pre-oxygenation by Baillard et al[1] represented the best trial on which to base our power calculation. That study was powered to detect a minimum difference in lowest arterial oxygen saturation during endotracheal intubation of 5 percent. The lowest arterial oxygen saturation in their intervention arm (non-invasive ventilation for pre-oxygenation, which has subsequently been considered standard-of-care for hypoxemic patients) was 93 percent with

a standard deviation of 8 percent. Recognizing the uncertainty in how the estimated standard deviation would translate to our study population, we employed a more conservative standard deviation estimate of 10 percent for our initial power calculation. In order to have 80 percent statistical power (using an alpha level of 0.05) to detect a difference in lowest oxygen saturation of 5 percent with a standard deviation of 10 percent, we needed to enroll a total of 128 patients.

Our comparison of the impact of apneic oxygenation versus usual care on lowest arterial oxygen saturation was factorialized with a comparison of video versus direct laryngoscopy with regard to successful intubation on the first attempt. As the enrollment of 150 patients was required to address the question of video versus direct laryngoscopy, we tested the detectable difference in lowest arterial oxygen saturation that would be provided by the enrollment of 150 patients across a range of standard deviations from 10 to 15 percent (Figure 1 in the Statistical Analysis Plan, included below).

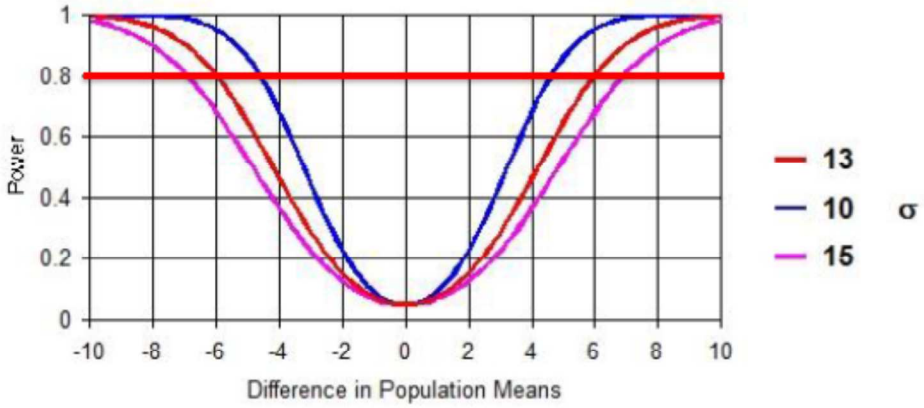

Figure 1. Detectable difference in lowest oxygen saturation at 80% power for three possible standard deviations in lowest oxygen saturation value.

Maintaining a desired power of 80 percent and alpha level of 0.05, enrollment of 150 patients would have allowed detection of a difference in lowest arterial oxygen saturation of 4.6 percent with an observed standard deviation of 10 percent, 5.0 percent with an observed standard deviation of 11 percent, 5.5 percent with an observed standard deviation of 12 percent, and 5.9 percent with an observed standard deviation of 13 percent. Acknowledging the uncertainty surrounding estimates of the anticipated standard deviation in our study population, we elected to target for the apneic oxygenation trial the same enrollment of 150 patients as for the factorialized comparison of video versus direct laryngoscopy. This more conservative approach accepted the risk of slightly over-powering the trial if our observed standard deviation were 10 percent (our

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chosen 'best case scenario') in order to minimize the risk of a significantly under-powered trial if our observed standard deviation were as high as 13 percent (our 'worst case scenario'). Because our final sample size was chosen to maintain a detectable difference in the desired range across a spectrum of possible standard deviations, we report the power calculation in the form of a detectable difference for the sample size we chose, at the anticipated standard deviation.

All sample size calculations were performed using the t-test function in the PS power and sample size program[2].

SUPPLEMENTAL TABLES

Table E1. Pre-laryngoscopy management.

Characteristic	Usual Care (n = 73)	Apneic Oxygenation (n = 77)	*P* Value
Induction medication*, No. (%)			
Etomidate	66 (90.4%)	72 (93.5%)	.56
Ketamine	2 (2.7%)	2 (2.6%)	>.99
Propofol	10 (13.7%)	2 (2.6%)	.02
Midazolam	4 (5.5%)	1 (1.3%)	.20
Neuromuscular blockade*, No. (%)			
Succinycholine	30 (41.1%)	26 (33.8%)	.40
Rocuronium	42 (57.5%)	47 (61.0%)	.74
Vecuronium	1 (1.4%)	0 (0.0%)	.49
None	1 (1.4%)	4 (5.2%)	.37
Ventilation between induction and laryngoscopy*, No. (%)			
None	17 (23.3%)	23 (29.9%)	.46
Bag-valve-mask	40 (54.8%)	38 (49.4%)	.52
BIPAP	17 (23.3%)	17 (22.1%)	>.99
Other	0 (0.0%)	1 (1.3%)	>.99
Laryngoscopy device used for first attempt†, No. (%)			.57
Direct laryngoscope	36 (49.3%)	40 (51.9%)	
McGRATH® MAC video laryngoscope	37 (50.7%)	36 (46.8%)	
GlideScope® GVL video laryngoscope	0 (0.0%)	1 (1.3%)	
Curved laryngoscope blade, No. (%)	71 (97.3%)	74 (97.4%)	>.99
Endotracheal tube size, median [IQR]	8 [8-8]	8 [8-8]	.29

Data are presented as median [25th percentile – 75th percentile] or number (percentage). Fewer patients in the apneic oxygenation arm received propofol for induction. Otherwise, there were no differences in pre-laryngoscopy airway management between the study groups.
*Patients could receive more than one.
†In each study arm, the first attempt at laryngoscopy was made with a size 4 blade in 78% of cases and a size 3 blade in 22% of cases.

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Table E2. Procedural characteristics.

	Usual Care (n = 73)	Apneic Oxygenation (n = 77)	*P* Value
Best Cormack-Lehane grade of view, No. (%)			.37
Grade I	48 (65.8%)	55 (71.4%)	
Grade II	21 (28.8%)	16 (20.8%)	
Grade III	3 (4.1%)	4 (5.2%)	
Grade IV	0 (0.0%)	2 (2.6%)	
Difficulty of intubation, No. (%)			.19
Easy	57 (78.1%)	61 (79.2%)	
Moderate	15 (20.5%)	11 (14.3%)	
Difficult	1 (1.4%)	5 (6.5%)	
Intubation on the first laryngoscopy attempt, No. (%)	49 (67.1%)	52 (67.5%)	.96
Number of laryngoscopy attempts, median [IQR]	1 [1-2]	1 [1-1]	.60
Time from induction to secured airway, median [IQR], seconds	150 [102-245]	132 [88-205]	.31
Endotracheal tube introducer used, No. (%)	17 (23.6%)	21 (27.3%)	.71
Laryngeal mask airway required, No. (%)	1 (1.4%)	1 (1.3%)	>.99
Second operator required, No. (%)	4 (5.5%)	5 (6.7%)	>.99
Procedural complications, No. (%)			
Aspiration	2 (2.7%)	0 (0.0%)	.24
Esophageal intubation	3 (4.1%)	2 (2.6%)	.68
Systolic blood pressure < 80 mm Hg	7 (9.6%)	8 (10.4%)	>.99
Cardiac arrest	1 (1.4%)	1 (1.3%)	>.99
Airway trauma	0 (0.0%)	1 (1.3%)	>.99

Data are presented as median [25th percentile – 75th percentile] or number (percentage). The Cormack-Lehane system classifies views obtained by direct laryngoscopy based on the structures seen with higher grades indicating more limited view. Best grade of view was defined as the best glottic view obtained at any point during the procedure. Grade of view, difficulty of intubation, and complications were reported by the operator and data was missing on grade of view for one patient in the usual care group. There were no significant differences in procedural characteristics between the two study groups.

Table E3. Multivariable models for lowest oxygen saturation relative to study group adjusting for saturation at induction (model 1) and baseline confounders (model 2).

Model 1	**Effect**	**95% Confidence interval**	***P* Value**
Apneic oxygenation	1.60	-2.63 - 5.82	.46
Saturation at induction, %	1.12	0.68 - 1.56	<0.001
Model 2	**Effect**	**95% Confidence interval**	***P* Value**
Apneic oxygenation	1.60	-2.63 - 5.82	.46
Saturation at induction, %	1.12	0.68 - 1.56	<0.001
Age (years)	0.05	-0.12 - 0.21	.56
Body mass index (kg/m^2)	-0.14	-0.42 - 0.13	.31
APACHE II score	0.25	-0.08 - 0.58	.14
Shock	-0.63	-7.26 - 6.00	.85
BiPAP	-1.46	-6.41 - 3.49	.56
Highest FiO2 in prior 6 hours	-4.79	-14.82 - 5.23	.35
Video laryngoscope	1.54	-4.13 - 7.22	.59
Operator experience	0.05	-0.06 - 0.15	.37

In multivariable linear regression models adjusting for oxygen saturation at the time of induction (model 1) and additional baseline confounders (model 2), treatment with apneic oxygenation compared to usual care increased the mean lowest oxygen saturation by 1.6%, which did not approach statistical significance (p=0.456). APACHE II is Acute Physiology and Chronic Health Evaluation II – ranging from 0 to 71 with higher scores indicating higher severity of illness; Shock is mean arterial pressure less than 65 mm Hg or vasopressor use; BiPAP is Bilevel Positive Airway Pressure; FiO2 is fraction of inspired oxygen; Operator experience is defined as prior intubations with the specific laryngoscopy device used. After generation of the multivariable model, an exploratory univariate analysis was undertaken comparing patients in either arm who experienced extreme desaturation defined as lowest arterial oxygen saturation less than 70% (n=16) to those who did not (n=132). There was no difference between those with and without extreme desaturation in age, gender, BMI, APACHE II score, indication for intubation, active comorbidities at the time of intubation, vasopressor receipt, BiPAP receipt, lowest oxygen saturation in the six hours prior, approach to pre-oxygenation, saturation at the time of induction, use of apneic oxygenation, use of video laryngoscopy, or prior experience of the operator overall or with the assigned device. Patients with and without extreme desaturation did differ in receipt of neuromuscular blockade (87.5% versus 97.7%, $P = 0.03$), induction with propofol (25.0% versus 6.1%, $P = 0.009$), incidence of grade I or II view (68.8% versus 89.2%, $P = 0.009$), incidence of a moderate or difficult airway (62.5% versus 16.7%, $P < 0.001$), rate of intubation on the first laryngoscopy attempt (25.0% versus 72.7%, $P < 0.001$), median number of laryngoscopy attempts (3 versus 1, $P < 0.001$), median time to intubation (498 versus 130 seconds, $P < 0.001$), use of an endotracheal tube introducer (50.0% versus 22.1%, $P = 0.015$), and need for a second operator (43.8% versus 1.5%, $P < 0.001$).

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Table E4. Protocol Violations

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Administrative Information						
Months since starting enrollment	2	5	6	7	10	11
Oxygenation strategy assigned	UC	UC	UC	UC	UC	AO
Oxygenation strategy received	AO	AO	AO	AO	AO	UC
Reason for violation recorded	Yes *	No	Yes †	No	Yes ‡	Yes §
Patient Characteristics						
Age (years)	56	52	43	44	61	65
Gender	Male	Male	Male	Male	Male	Male
Body Mass Index (kg/m^2)	27.9	22.7	23.0	22.2	26.5	27.0
APACHE II score	6	15	14	19	14	16
BiPAP use in prior 6 hours	No	No	No	No	No	Yes
Highest FiO^2 in prior 6 hours	0.36	0.21	0.27	0.66	0.33	0.5
Lowest saturation in prior 6 hours	90	92	96	87	87	95
Operator Characteristics						
Number of prior intubations	150	68	128	69	69	150
Months of fellowship training	32.73	23.4	25.3	13.77	16.4	42.17
Procedural Characteristics						
Oxygen saturation at induction, %	91	96	99	90	99	100
Lowest oxygen saturation, %	38	95	98	84	97	96
Laryngoscopy device used	Video	Video	Video	Direct	Video	Video
Cormack-Lehane grade of view	Grade 1	Grade 1	Grade 1	Grade 1	Grade 1	Grade 1
Difficulty of Intubation	Easy	Easy	Easy	Easy	Easy	Easy
Number of laryngoscopy attempts	1	1	1	1	1	1
Time to intubation (sec)	70	110	25	120	155	104

Raw data are presented for the six patients in whom the assigned oxygenation strategy was not received. UC is usual care, AO is apneic oxygenation, Acute Physiology and Chronic Health Evaluation II – ranging from 0 to 71 with higher scores indicating higher severity of illness, BiPAP is Bilevel Positive Airway Pressure, FiO2 is fraction of inspired oxygen, Video is video laryngoscopy, Direct is direct laryngoscopy.
* Team failed to remove nasal cannula used for pre-oxygenation before induction
† IV tubing burst as induction meds pushed, nasal cannula from pre-oxygenation left in place and patient intubated immediately
‡ High Flow Nasal Cannula from pre-oxygenation accidently left in place throughout procedure
§ Randomized to 15LC apneic oxygenation but this was NOT placed (patient on BiPAP and team intended to place but neglected to after drugs pushed)

Table E5. Per-protocol analysis.

	Apneic Oxygenation not received	Apneic Oxygenation received	
	(n = 68)	(n = 80)	
Procedural Outcomes			***P* Value**
Lowest oxygen saturation, median [IQR], %	90 [80-96]	92 [84-98]	.21
Lowest oxygen saturation < 90% No. (%)	32 (47.1%)	36 (45.0%)	.87
Lowest oxygen saturation < 80% No. (%)	17 (25.0%)	13 (16.3%)	.22
Decrease in oxygen saturation, median [IQR], %	4.5 [0.5-14.0]	4.0 [0.0-12.0]	.61
Decrease in oxygen saturation > 3% No. (%)	39 (57.4%)	42 (52.5%)	.62
Clinical Outcomes			
Duration of ventilation, median [IQR], days	3 [2-7]	3 [1-10]	.58
Intensive care unit length of stay, median [IQR], days	7 [3-10]	4 [2-8]	.20
Died within one hour of intubation No. (%)	1 (3.0%)	0 (0.0%)	>.99
Died before hospital discharge No. (%)	33 (47.8%)	30 (37.0%)	.19

Data are presented as median [25th percentile – 75th percentile] or number (percentage).

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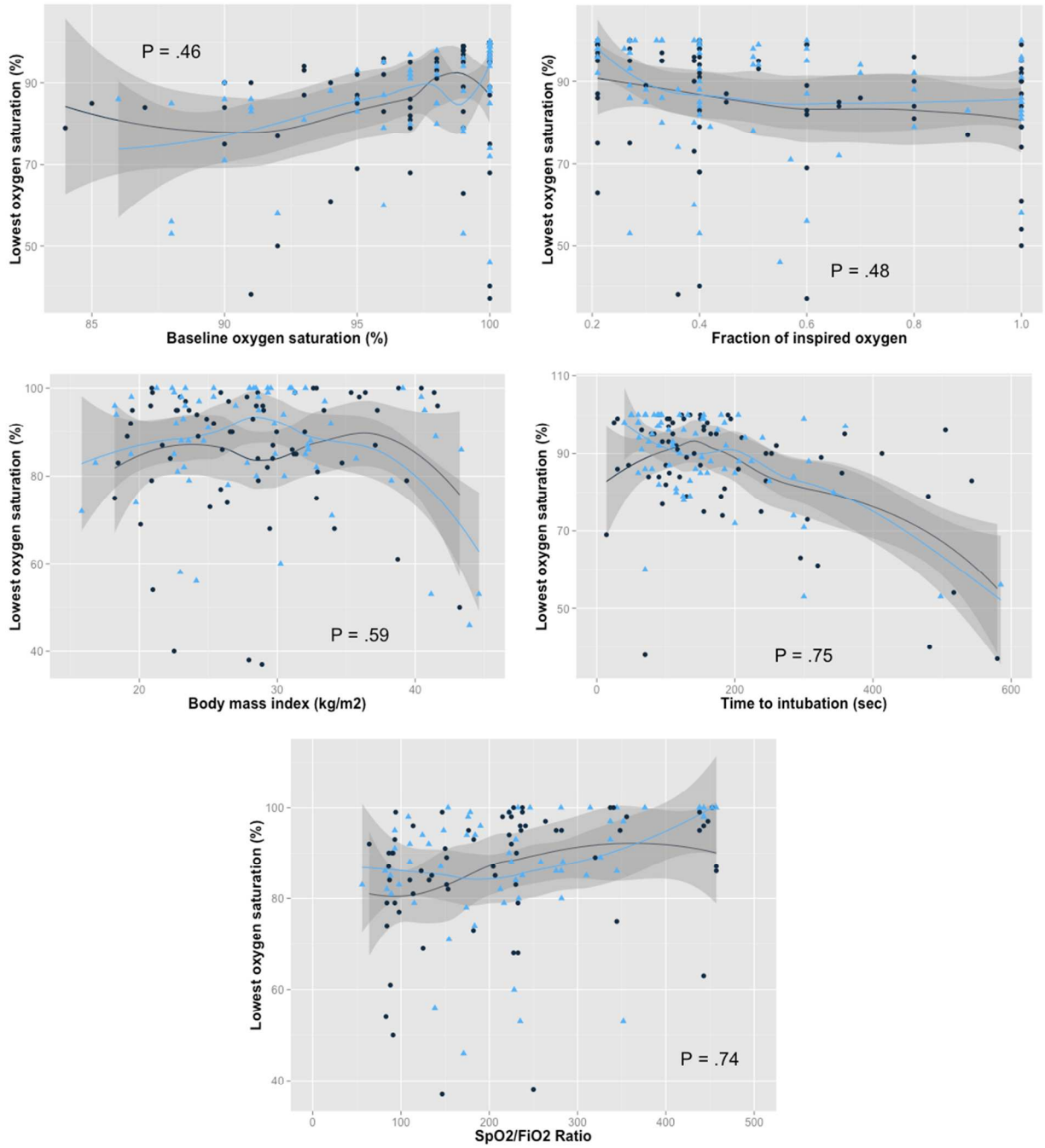
Table E6. Operator compliance with best-practices in airway management.

	(n = 23)
Pre-oxygenation device in place*, No. (%)	23 (100%)
Difficult airway equipment immediately available†, No. (%)	23 (100%)
Yankauer suction instrument checked for function, No. (%)	23 (100%)
Intravenous access checked for function, No. (%)	23 (100%)
Laryngoscope and endotracheal tube checked for function, No. (%)	21 (91.3%)
End-tidal carbon dioxide detector visualized‡, No. (%)	20 (87.0%)
Specific roles assigned§, No. (%)	21 (91.3%)
Assessment of airway difficulty verbalized, No. (%)	21 (91.3%)
Intubation drug selection and contraindications verbalized, No. (%)	23 (100%)
Attending physician present, No. (%)	23 (100%)
Patient position	
Completely flat, No. (%)	6 (26.1%)
Sniffing position, No. (%)	10 (43.5%)
Shoulders ramped, No. (%)	4 (17.4%)
Head-of-bed ramped, No. (%)	1 (4.3%)
Other, No. (%)	2 (8.7%)

Data are presented as number (percentage). In a convenience sample of intensive care unit intubations, independent observers graded compliance of the intubating fellow with best-practices in emergent airway management.
*Pre-oxygen devices included standard nasal cannula, high-flow nasal cannula, non-rebreather mask, and bilevel positive airway pressure
†Difficult airway equipment including video laryngoscope, endotracheal tube introducer, laryngeal mask airway, and cricothyrotomy kit was contained in an "airway bag" which was considered immediately available if open and inside the room at the time of induction.
‡End-tidal carbon dioxide detectors were packaged with laryngoscope blades and endotracheal tubes and present in the room prior to every intubation. However, they were only considered visualized when removed from the packaging and placed within the visual field of the operator.
§Roles included nurse administering induction medications, respiratory therapist in charge of bag-mask ventilation, and second operator.

SUPPLEMENTAL FIGURES

Figure E1. Lowest oxygen saturation by patient and procedure characteristics.



The primary outcome of lowest arterial oxygen saturation is displayed for each patient randomized to apneic oxygenation (blue triangles) and usual care (black circles). *P* values are for the interaction between study group assignment and the variable on the x-axis after accounting for confounders. There was no baseline oxygen saturation, fraction of inspired oxygen in the 6 hours prior to induction, ratio of oxygen saturation to fraction of inspired oxygen ($SpO2/FiO_2$ ratio), or time to intubation for which a significant difference in lowest oxygen saturation between apneic oxygenation and usual care was present. $SpO2/FiO_2$ ratio is among 132 patients with saturation < 97% in the 6 hours prior to intubation.

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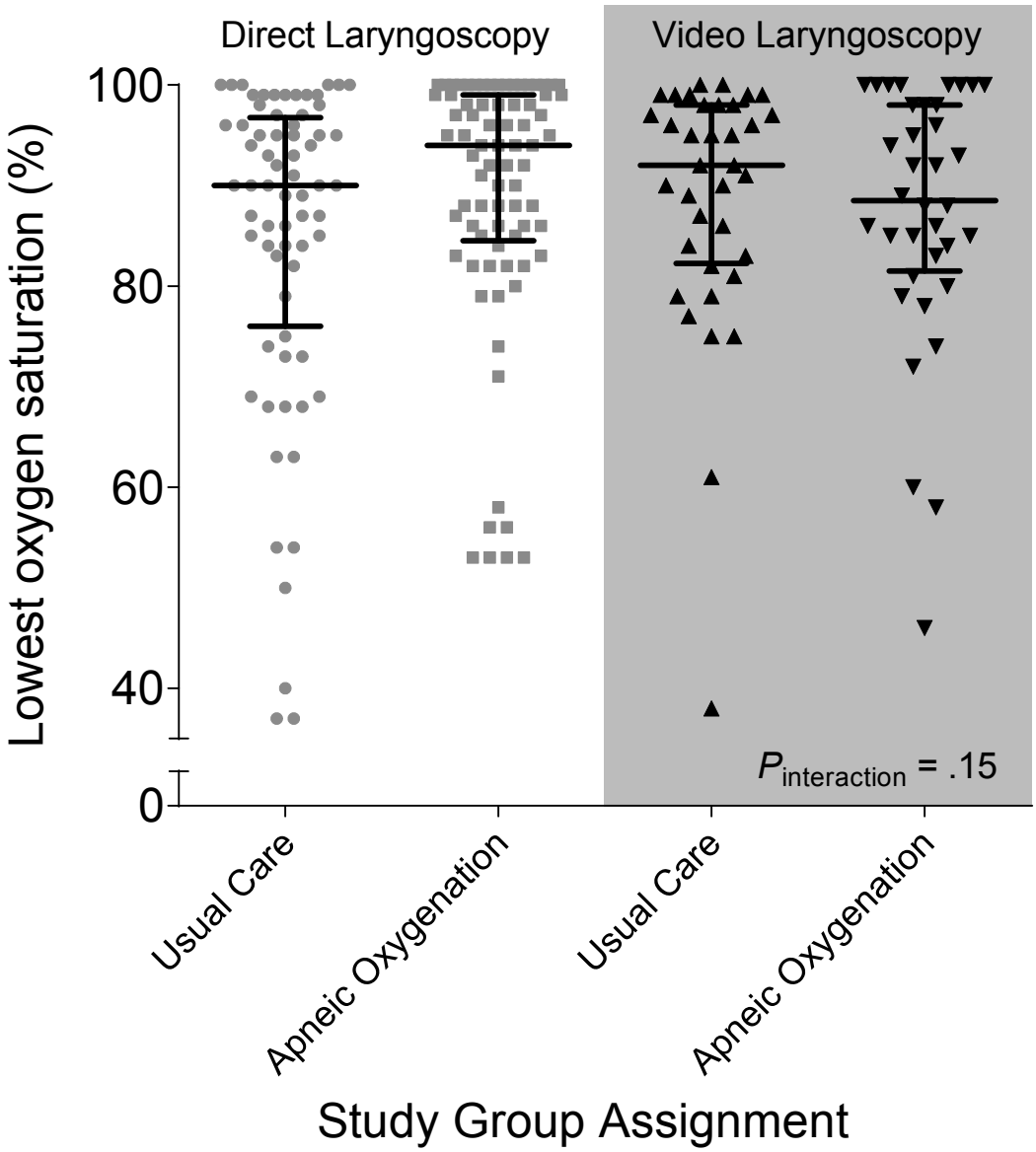
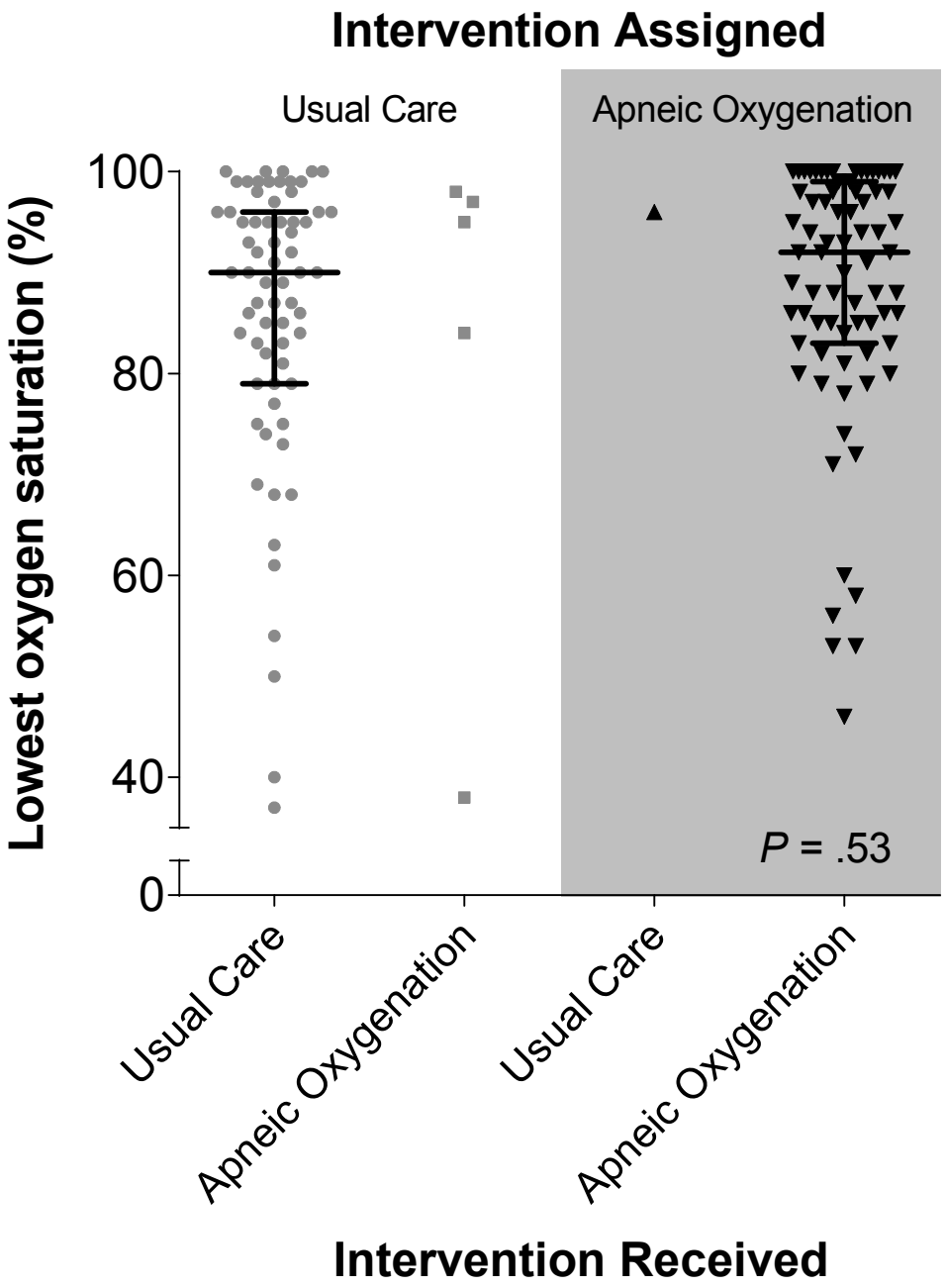
Figure E2. Lowest arterial oxygen saturation by factorialized group assignment.



The primary outcome of lowest arterial oxygen saturation between induction and two minutes after completion of endotracheal intubation is displayed for patients randomized to apneic oxygenation versus usual care within each laryngoscopy device arm. Median and interquartile range are displayed. There was no significant interaction between laryngoscopy device assignment and the effect of apneic oxygenation or usual care on lowest arterial oxygen saturation.

Figure E3. Lowest arterial oxygen saturation by intervention assigned and received.



The primary outcome of lowest arterial oxygen saturation between induction and two minutes after completion of endotracheal intubation is displayed by the oxygenation intervention assigned and received. Median and interquartile range are displayed. There was no significant difference in mean lowest arterial oxygen saturation between the four groups by the Kruskal-Wallis test.

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SUPPLEMENTAL REFERENCES

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2. Dupont WD, Plummer W. PS power and sample size program available for free on the Internet. *Control. Clin Trials* 1997;18:274.