Automated Alerting and Recommendations for the Management of Patients with Preexisting Hypoxia and Potential Acute Lung Injury

A Pilot Study

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ABSTRACT

Background: Acute lung injury (ALI) is associated with high mortality. Low tidal volume (Vt) ventilation has been shown to reduce mortality in ALI patients in the intensive care unit. Anesthesiologists do not routinely provide lung-protective ventilation strategies to patients with ALI in the operating room. The authors hypothesized that an alert, recommending lung-protective ventilation regarding patients with potential ALI, would result in lower Vt administration.
Methods: The authors conducted a randomized controlled trial on anesthesia providers caring for patients with potential ALI. Patients with an average or last collected ratio of partial pressure of arterial oxygen to inspired fraction of oxygen less than 300 were randomized to providers being sent an alert with a recommended Vt of 6 cc/kg predicted body weight or conventional care. Primary outcomes were Vt/kg predicted body weight administered to patients. Secondary outcomes included ventilator parameters, length of postoperative ventilation, and death.

Results: The primary outcome was a clinically significant reduction in mean Vt from 508–458 cc ($P = 0.033$), with a reduction in Vt when measured in cc/kg predicted body weight from 8 to 7.2 cc/kg predicted body weight ($P = 0.040$). There were no statistically significant changes in other outcomes or adverse events associated with either arm.
Conclusions: Automated alerts generated for patients at risk of having ALI resulted in a statistically significant reduction in Vt administered when compared with a control group. Further research is required to determine whether a reduction in Vt results in decreased mortality and/or postoperative duration of mechanical ventilation.

What We Already Know about This Topic

- Low tidal volume ventilation (6 ml/kg) improves survival in patients with acute respiratory distress syndrome, yet when such individuals receive anesthesia, higher tidal volumes are typically used

What This Article Tells Us That Is New

- In an open-label parallel arm study of 100 patients with acute respiratory distress syndrome receiving low tidal volume ventilation, sending the anesthesia providers an alert with a recommended tidal volume of 6 ml/kg resulted in a significant reduction in tidal volume delivered during anesthesia compared with conventional care
- Complications and major morbidity did not differ between groups

ACUTE lung injury (ALI) is a devastating condition with significant mortality. The clinical syndromes of ALI and acute respiratory distress syndrome (ARDS) are defined by descriptive clinical findings, regardless of the specific etiology of acute pulmonary dysfunction. The American–European Consensus Committee in 1994 defined clinical ALI as requiring, (1) respiratory failure of acute onset, with a ratio of partial pressure of arterial oxygen (Pa_{O_2}) to inspired fraction of oxygen (F_{IO2}) (Pa_{O_2}/F_{IO2} or P/F) less than 300 mmHg (regardless of the level of positive end-expiratory pressure [PEEP]), (2) bilateral infiltrates on frontal chest radiograph, and (3) a pulmonary capillary wedge pressure less than 18 mmHg (if measured) or no evidence of left atrial hypertension.[1]

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ARDS was defined identically, except for a lower limiting value of less than 200 mmHg for Pao_2/Fio_2.[1] ALI and ARDS affect a large number of patients and have a poor prognosis. The incidence of ALI/ARDS has been variably reported to be 50,000–190,000 cases per year in the United States.[1–7]

The only ventilator intervention to date that has clearly demonstrated a survival benefit in controlled studies in adults with ARDS has been the adoption of a low tidal volume ventilation strategy (6 ml/kg predicted body weight [PBW]) with plateau pressures less than 30 cm H_2O.[8] Additionally, the use of recruitment maneuvers, higher levels of PEEP, and judicious administration of fluids have been shown to reduce ventilator days, and increase Pao_2, while avoiding potential hyperoxia-induced lung injury.[9–12] Together, these methods comprise a lung-protective ventilation strategy (LPVS). A number of animal and clinical studies have shown that resorting to a nonprotective strategy, by adoption of high tidal volumes or higher plateau pressures, can result in serious lung injury and in some cases, parallel the course of patients with severe ARDS.[13,14]

Despite dissemination of this management strategy, we have recently found that LPVSs were not specifically undertaken in patients with ALI in the operating room setting.[15] Of 1,286 patients who underwent procedural anesthesia with a $Pao_2/Fio2$ ratio less than 300, 242 met the criteria for diagnosis of ALI before the procedure. Intraoperative lung-protective ventilator management was not routinely performed on these patients. Patients, on average, received 8.5 cc/kg PBW ventilation and approximately 5 cm H_2O of PEEP with high Fio_2. Typically, these patients had higher Pao_2 and tidal volumes in the operating room compared with the preanesthetic setting.

In the current study, we tested the hypothesis that information to anesthetic providers of recommended ventilation strategy for potential ALI in patients with low preoperative P/F ratios would result in an increased use of lower tidal volumes and higher PEEP consistent with a LPVS.

Materials and Methods

Institutional Review Board approval was obtained for this randomized, open-label, parallel arm clinical trial from the Institutional Review Boards of the University of Michigan Medical School (Ann Arbor, MI), under waiver of consent without use of a data safety monitoring board, due to the low-risk nature of the study. Figure 1 depicts the flow of patients through the trial. The study was conducted at a single site, the University of Michigan Medical Center. Patients were recruited using a "just-in-time" automated anesthesia information management system (Centricity, Wishahaka, WI) script, which was created to screen all patients undergoing an anesthetic at the time of the start of anesthesia or entry into the operating room, with central laboratory arterial blood gases collected in the past 2 days. From these arterial blood gases, the average P/F ratio was calculated for each patient. If the patient was 18 yr old or more, the average P/F ratio was less than 300 or the last P/F ratio was less than 300, and a valid history and physical, including the patient's height, was present. Patients were enrolled and randomized, using a real-time electronic pseudorandom number generator to intervention or no intervention (control) in a 1:1 allocation ratio, to enroll two equal groups of 50 patients. No system of stratification was used during randomization. If randomized

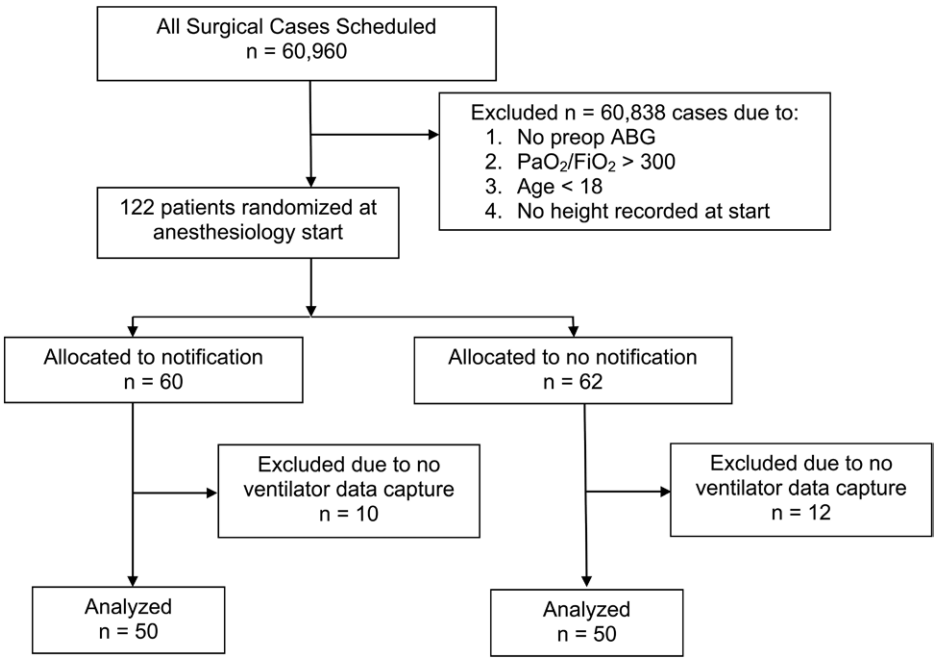


Fig. 1. Method of case exclusion. ABG = arterial blood gas; $Pao_2/Fio2$: respiratory failure of acute onset with a ratio of partial pressure of arterial oxygen (Pao_2) to inspired fraction of oxygen ($Fio2$) ($Pao_2/Fio2$) ratio.

to intervention, the height of the patient was obtained from the electronic history and physical, and the PBW was calculated. An automated text page was sent to the attending anesthesiologist's and/or in-room provider's hospital pager, depending on "signed in" status at either start of anesthesia, or at the time the patient was in the operating room, stating:

"Patient: LAST, FIRST has a P/F ratio consistent with acute lung injury. If this patient has ALI, recommended tidal volume is <XXX>cc. Recommended PEEP and Fio2 are shown on the Web site."††

There was no protocol-based care in this study. All clinical decisions were left to the discretion of the anesthetic care team, who could decide whether to follow the recommendations of the automated alert. The anesthesia machine used in this study was the Aisys (General Electric Healthcare, Milwaukee, WI). This machine provides basic volume control ventilation, in addition to advanced pressure control modes, pressure control mode with a volume guarantee, pressure support, and inverse ratio ventilation. Only basic ventilator information was collected by the anesthesia information management system, including delivered tidal volume, PEEP, peak inspiratory pressure, respiratory rate, and $F_{IO}2$. No recommendation on ventilator mode was included in the alert, and the ventilator mode was not recorded.

The study was intended to demonstrate the superiority of the alert group, with a reduction in the total cc/kg PBW administered. The primary outcome measure was median tidal volume in cc/kg PBW between the two groups, from surgical incision to dressing completed. Secondary outcomes included median total tidal volumes, PEEP, and peak inspiratory pressure. Finally, we calculated what would have been the recommended LPVS tidal volumes for the patients not receiving the alert (control group) and compared these tidal volumes with the actual tidal volumes administered, to determine the mean difference. After the completion of enrollment and initial statistical analysis, the preoperative anesthetic records were reviewed for common conditions, which have been associated with increased morbidity and mortality. Additionally, preoperative chest radiographs were examined, if available, to look for the presence of bilateral infiltrates that would be consistent with a diagnosis of ALI. Radiograph review was completed using a consensus process by the investigators while they were blinded to additional information about the patients. Finally, the hospital course of each patient was examined for postoperative complications, which could be associated with low tidal volume ventilation, including prolonged intubation, stroke/herniation, myocardial infarction, new onset renal failure, and death.

Statistics

The study was designed with a sample size of 50 patients in each group to have 80% power to detect a difference in means of 1.0 cc/kg PBW, assuming that the common SD was 1.00 cc/kg PBW, using a two-sided independent *t* test ($\alpha = 0.05$). Comparison between groups was made with SPSS version 18 (SPSS Software, Chicago, IL) and R version 2.16 (R Foundation for Statistical Research, Vienna, Austria), using the two-tailed Student's *t* test and/or Mann–Whitney U test for continuous variables or chi-square analysis for dichotomous variables. *P* values less than 0.05 were considered to be statistically significant.

Results

We successfully enrolled and collected data on 100 patients (fig. 1). The study enrolled from July 8, 2010 until February 21, 2011. Twenty-two patients were excluded from the dataset after randomization due to lack of ventilator data capture. No other data were missing in the dataset that was collected. There were no statistically significant differences between comorbidities in the control and intervention groups (table 1). For the 50 patients enrolled in the intervention group, the average recommended tidal volume was 390 cc. The mean PBW in both populations was 65 kg. The intervention group received lower total tidal volumes (458 *vs.* 508 cc; $P = 0.033$) and lower tidal volumes per kilogram of PBW (7.19 *vs.* 7.97 cc/kg; $P = 0.040$; fig. 2). The distribution of the low tidal volume cc/kg PBW was not entirely normal, as such we examined it using both the Mann–Whitney U test and *t* test, which provided *P* values of 0.040 and 0.058, respectively.

There was no statistical difference in the PEEP or peak inspiratory pressure between the two groups. These data are summarized in table 2 and figure 2. Patients in the intervention group received total tidal volumes closer to the recommended tidal volumes than those in the intervention group (mean difference 67 cc [95% CI, 33–101] *vs.* 117 cc [95% CI, 81–153]; $P = 0.046$). The absolute value of the difference in patients who received the alert was 109 cc (95% CI, 86–133), which was lower than the absolute value of 147 cc (95% CI, 121–173) in those patients who did not receive the alert ($P = 0.034$). There were also more patients in the intervention group who received tidal volumes less than 6.5 cc/kg PBW (17 patients *vs.* 8 patients; $P = 0.065$), although this did not meet statistical significance. On review of all cases, there was no statistically or clinically increased rate of complications associated with the intervention group. This included a statistically identical number of postoperative ventilator days, strokes, myocardial infarctions, and deaths. These data are further illustrated in table 2.

On review of the initial dataset, three patients were found to have profoundly low tidal volumes of less than 3 cc/kg PBW, and three were found to be of The American Society of Anesthesiologists Physical Status 6. A sensitivity analysis was completed excluding these patients from the dataset (tables 3 and 4). Overall, there were no statistically significant changes in the results.

†† http://anes.med.umich.edu/ARDStable.html. The Web site is no longer active. On the site was a copy of the ARDSnet ARMA protocol PEEP table.

Table 1. Demographics and Comorbidities Between Intervention and Control Groups

	Intervention n = 50	Control n = 50
Age, yr	60.5 (53.0–67.0)	56.5 (44.3–64.8)
Predicted body weight	63.9 (57.0–72.4)	68.4 (55.0–73.0)
ASA status	4 (3–4)	4 (3–4)
Preoperative P/F ratio	198.8 (168.3–231.7)	184.5 (139.5–215.4)
Male	30 (60)	33 (66)
Emergent surgery	17 (34)	21 (42)
Hypertension	29 (58)	25 (50)
CAD	20 (40)	15 (30)
CHF	8 (16)	16 (32)
Pneumonia	7 (14)	6 (12)
COPD	11 (22)	9 (18)
Asthma	2 (4)	2 (4)
OSA	10 (20)	11 (22)
Hepatic disease	8 (16)	13 (26)
Renal failure	17 (34)	18 (36)
Diabetes	16 (32)	14 (28)
Bilateral infiltrates on CXR	37 (74)	33 (66)

There were no statistically significant differences between groups in any parameter. Values are represented as median (IQR) or n (%).
ASA = American Society of Anesthesiologists; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CXR = chest x-ray; P/F = ratio of partial pressure of arterial oxygen to inspired fraction of oxygen; OSA = obstructive sleep apnea.

Discussion

In this prospective randomized controlled trial, an automated intraoperative notification alerting clinicians to the potential presence of ALI/ARDS led to statistically significant reduction in delivered total median tidal volumes and in volumes measured in cc/kg PBW. There were no differences in the PEEP between the two groups. This is the first trial that we are aware of that changed clinician behaviors in patients with possible ALI in the perioperative environment.

ALI is an established syndrome that has profound effects on numerous patients each year. The incidence of ALI in two recent studies has been estimated at 22–86 cases per 100,000 persons per year,[5,7] with 40–43% of these patients having ARDS.[7] Survival statistics for patients with ALI/ARDS vary with lung injury etiology and age, but overall mortality rates in both adult and pediatric patients remain substantial at 20–50%, despite sophisticated intensive care.[2,3,5–7,16–19] The significance of distinguishing between the two clinical syndromes in a practical sense is uncertain, because a meta-analysis of 102 studies before 1996 showed little or no difference in mortality rates between patients meeting criteria for ALI compared with ARDS.[20] This was also the conclusion in the recent NEJM article by Rubenfeld *et al.*,[7] which reported mortality rates of 38.5% for ALI and 41% for ARDS, with an estimated 74,500 deaths per year, and an aggregate 3.6 million hospital days of care in the United States.

Over the past 2 decades, a variety of interventions and intensive care strategies have been used in treating patients with ALI/ARDS. Historically, ALI/ARDS was treated with large tidal volumes and high peak pressures, in an attempt to improve oxygenation. However, it has been shown that such efforts actually add to ventilator-induced lung injury through multiple mechanisms, including alteration of the pulmonary cytoskeleton, disturbed alveolar fluid balance, and increased inflammatory response.[21–25] Current standard of care for ARDS includes mechanical ventilation, with adoption of lung protective strategies, judicious fluid management, adjunct nutritional support, and more importantly the diagnosis and treatment of the underlying cause. Despite this care, the only multicenter randomized controlled evidence for reducing ARDS-associated mortality consists of a reduction in tidal volumes from 12 to 6 cc/kg PBW and the administration of neuromuscular blockade for 48 h after the onset of the syndrome.[26]

The application of relatively low tidal volumes during anesthesia is not a new concept and has been advocated in thoracic anesthesia, where ALI is a devastating and common diagnosis. In work by Licker,[27] it was determined that increased tidal volumes were associated with the development of ALI. Subsequent work showed that protocol-based care, with reduced tidal volumes in thoracic oncologic surgery during one-lung ventilation, reduced the incidence of ALI from 3.7 to 0.9%.[28] However, Licker's prevention trial was conducted in nonrandomized patients without ALI, undergoing only a single-type procedure and did not address the management of patients with preexisting ALI.

Recently, we have shown that patients meeting criteria for ALI preoperatively are managed in a similar format to those who undergo anesthesia with hypoxia for another

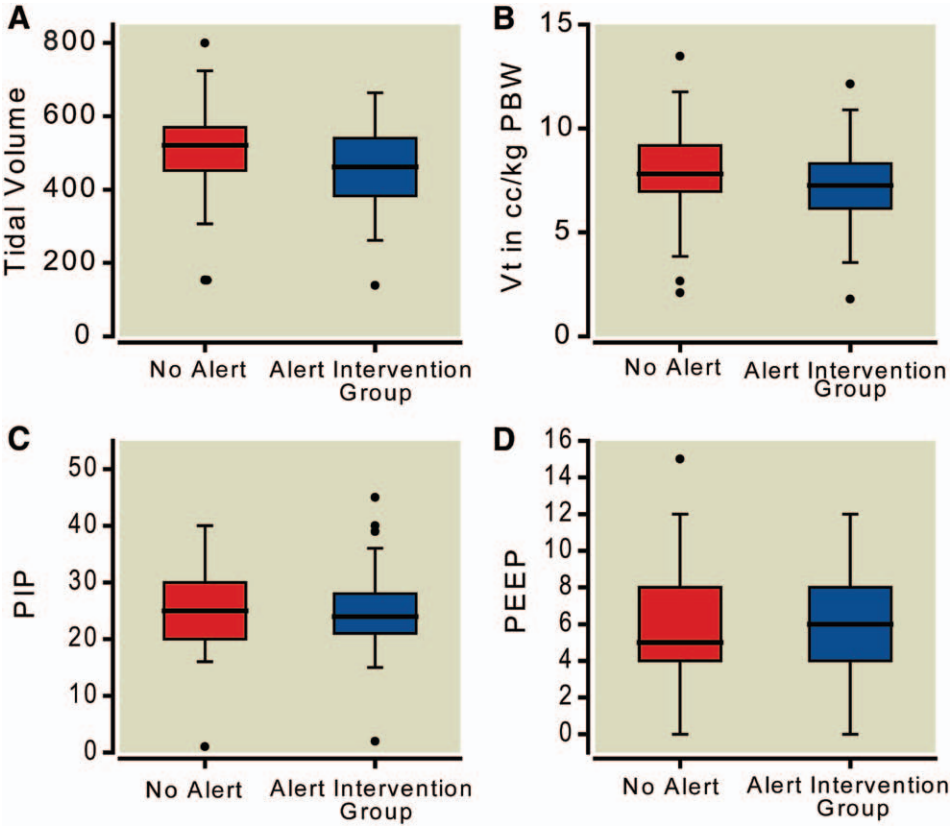


Fig. 2. (*A–D*) Distribution of ventilator settings by intervention status. (*A*) Tidal volume (Vt) in cc by intervention status. *Solid lines* represent median values, *boxes* represent the interquartile range, *T bars* represent 95% of total sample, ○ represent outliers (1.5–3× box length), and • represent extreme outliers (>3× box length). (*B*) Vt in cc/kg predicted body weight (PBW) by intervention status. *Solid lines* represent median values, *boxes* represent the interquartile range, *T bars* represent 95% of total sample, represent outliers (1.5–3× box length), and • represent extreme outliers (>3× box length). (*C*) Peak inspiratory pressure (PIP) by intervention status. *Solid lines* represent median values, *boxes* represent the interquartile range, *T bars* represent 95% of total sample, represent outliers (1.5–3× box length), and • represent extreme outliers (>3× box length). (*D*) Positive end-expiratory pressure (PEEP) by intervention status. *Solid lines* represent median values, *boxes* represent the interquartile range, *T bars* represent 95% of total sample, represent outliers (1.5–3× box length), and • represents extreme outliers (>3× box length).

reason.[15] This care frequently mirrors the care provided in the intensive care unit before their procedure, with an important exception that patients receiving LPVS with tidal volumes less than 6 cc/kg PBW, received significantly increased tidal volumes intraoperatively. Although the reason for this difference in practice is unknown, the current study shows that an automated alert triggered by P/F ratios can increase compliance with a LPVS for patients

Table 2. Intraoperative Differences and Postoperative Outcomes

	Intervention n = 50	Control n = 50	*P* Value
Median Vt	462 (383.5–539.3)	522.5 (455.3–573.8)	0.014
Median weight-adjusted Vt, cc/kg PBW	7.3 (6.2–8.3)	7.8 (7.0–9.1)	0.032
Median PIP	24 (21–27.5)	25 (20–29.8)	0.849
Median PEEP	6 (4.0–8.0)	5 (4.3–8.0)	0.652
Postoperative ventilator days	3 (1–5)	3 (1–9)	0.325
Mortality at 28 d	8 (16)	6 (12)	0.774
Postoperative stroke/herniation	1 (2)	1 (2)	1.000
Postoperative MI	0 (0)	2 (4)	0.495
Postoperative new AKI/dialysis	4 (8)	6 (12)	0.741

Values are represented as average (IQR) or n (%).

AKI = acute kidney injury; MI = myocardial infarction; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; Vt = tidal volume.

Table 3. Demographics and Comorbidities Between Intervention and Control Groups After Exclusion of Ultra Low Tidal Volumes

	Intervention n = 47	Control n = 47
Age, yr	63 (53.5–67.5)	57 (45.5–64.5)
Predicted body weight	63.9 (57.0–71.9)	68.4 (55.3–74.2)
ASA status	4 (3–4)	4 (3–4)
Preoperative P/F ratio	201 (176.1–230.9)	184.8 (140.2–221.3)
Male	29 (62)	30 (64)
Emergent surgery	15 (32)	18 (38)
Hypertension	27 (57)	25 (53)
CAD	20 (43)	15 (32)
CHF	8 (17)	16 (34)
Pneumonia	7 (15)	6 (13)
COPD	11 (23)	9 (19)
Asthma	2 (4)	2 (4)
OSA	10 (21)	10 (21)
Hepatic disease	6 (13)	12 (26)
Renal failure	16 (34)	17 (36)
Diabetes	15 (32)	14 (30)
Bilateral infiltrates on CXR	36 (72)	31 (62)

There were no statistically significant differences between groups in any parameter. Values are represented as median (IQR) or n (%).

ASA = American Society of Anesthesiologists; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CXR = chest x-ray; P/F = ratio of partial pressure of arterial oxygen to inspired fraction of oxygen; OSA = obstructive sleep apnea.

who may have ALI. This is especially important for patients undergoing nonthoracic surgeries, where ALI may not be a foremost concern for anesthetic providers and is likely underdiagnosed.

We have demonstrated that a single pager notification that simply suggests the institution of a LPVS can impact provider behavior regards to intraoperative management of patients at risk for ALI. Notifications, such as those in this pilot study, may be an effective way to intervene and reduce the potential for further injury in patients with ALI. However, it is important to allow clinicians the flexibility to selectively implement a set of recommendations rather than protocolize care because situations where it is either impractical, or unsafe to follow a set of predefined recommendations may occur. For example, in a patient at risk for ALI with underlying pulmonary dysfunction as well as concomitant head injury and increased intracranial pressures, low tidal volumes with permissive hypercapnea may be contraindicated. These complex clinical situations may have contributed to the nonadherence to strict LPVS in this study. For example, this may be the reason for lower PEEP values than were recommended by the table on the Web site. As increasing PEEP may cause hemodynamic compromise, providers may have been concerned about applying PEEP above a certain level in these potentially critically ill patients.

Table 4. Intraoperative Differences and Postoperative Outcomes After Exclusion of Ultra Low Tidal Volumes

	Intervention n = 47	Control n = 47	*P* Value
Median Vt	464 (391–539)	525 (488–580)	0.003
Median weight-adjusted Vt, cc/kg PBW	7.3 (6.2–8.3)	7.8 (7.0–9.0)	0.02
Median PIP	24 (21–27)	25 (20–30)	0.674
Median PEEP	6 (4–8)	5 (4–8)	0.571
Postoperative ventilator days	3 (1–5)	3 (1–9)	0.945
Mortality at 28 d	6 (13)	5 (11)	1.000
Postoperative stroke/herniation	1 (2)	1 (2)	1.000
Postoperative MI	0 (0)	2 (4)	0.495
Postoperative new AKI/dialysis	4 (9)	5 (11)	1.000

Values are represented as average (—) or n (%).

AKI = acute kidney injury; MI = myocardial infarction; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; Vt = tidal volume.

Our study has several limitations, which are important to discuss. First, the trial was undertaken at a single center with a relatively small number of patients. These results and the changes in provider behavior may not be generalizable to other settings. In particular, the study relied on the relatively advanced anesthesia information management system architecture in place at the study hospital, although most centers with an anesthesia information management system should be able to replicate the notifications. This is notable, as this study design introduces a new method of studying the impact of low-risk clinical reminders on care in ALI and other conditions, which is consistent with the highest level of medical evidence, the randomized controlled trial. This minimizes the concerns frequently associated with pre- and postanalysis that is common in quality improvement literature.

Second, in this study, we enrolled patients based on only one of the three criteria for ALI; because the study was performed with a "just-in-time," automated screening and enrollment strategy that would be replicable at other centers, it was not possible to obtain intravascular volume status or chest radiograph information to confirm a diagnosis of ALI before the anesthetic. However, previous work has shown that lower tidal volumes can also help prevent the development of ALI.[27,28] Therefore, interventions that lower tidal volumes may be beneficial to any patient with a low P/F ratio, regardless of whether the other criteria for ALI are met.

Finally, Although there was an attempt made to determine whether the outcomes were different between the two groups, the study was distinctly underpowered to detect a subtle increase in complications from implementation of the reminder intervention. Further studies assessing the impact of these types of interventions are therefore, warranted.

In conclusion, we have demonstrated that anesthesiologists will modify their intraoperative ventilation strategies when notified about the potential risk for ALI underlying preoperative hypoxia. This relatively simple alert system is a potentially useful tool to bring provider behavior more in-line with the most recent standards of care from the literature. It would be reasonable to undertake a multicenter prospective trial in the future to determine the influence this type of notification can have on morbidity and mortality.

References

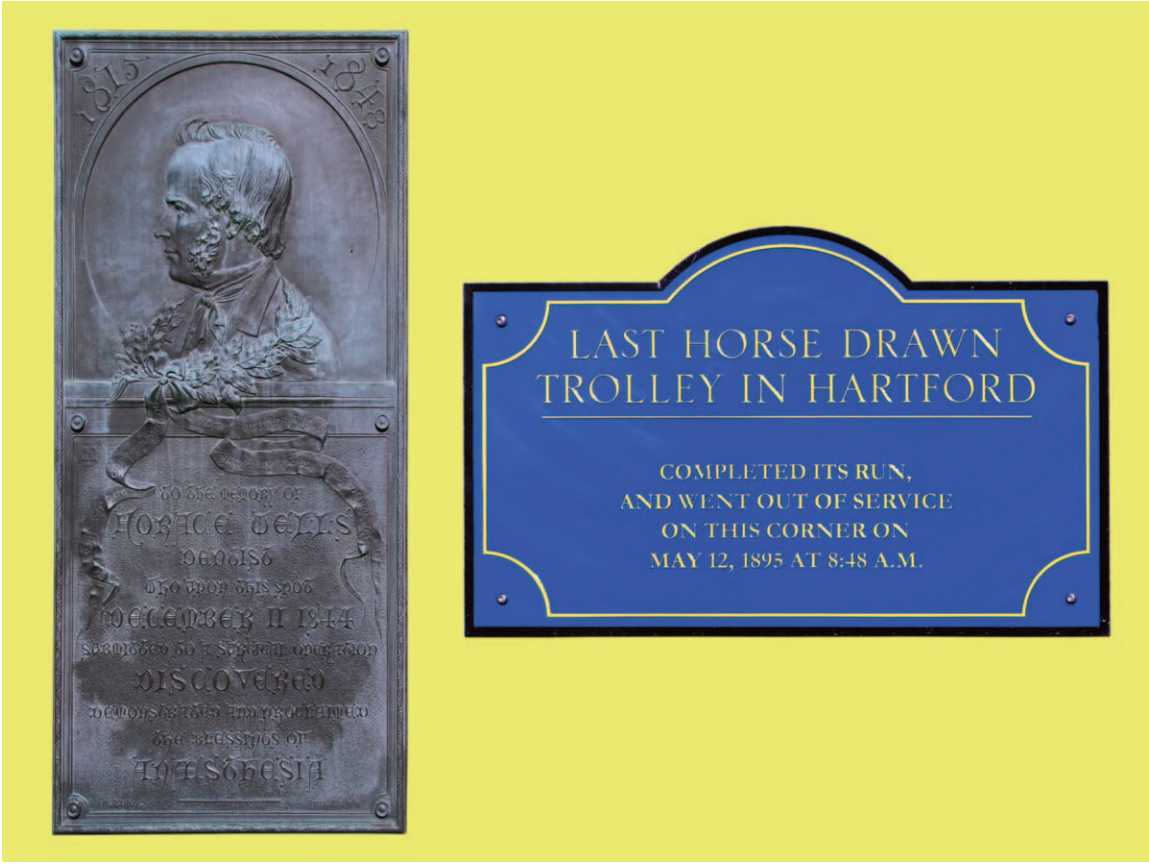
1. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149(3 Pt 1):818–24
2. Hudson LD, Milberg JA, Anardi D, Maunder RJ: Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1995; 151(2 Pt 1):293–301
3. Ware LB, Matthay MA: The acute respiratory distress syndrome. N Engl J Med 2000; 342:1334–49
4. Bersten AD, Edibam C, Hunt T, Moran J; Australian and New Zealand Intensive Care Society Clinical Trials Group: Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. Am J Respir Crit Care Med 2002; 165:443–8
5. Goss CH, Brower RG, Hudson LD, Rubenfeld GD; ARDS Network: Incidence of acute lung injury in the United States. Crit Care Med 2003; 31:1607–11
6. Rubenfeld GD: Epidemiology of acute lung injury. Crit Care Med 2003; 31(4 suppl):S276–84
7. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD: Incidence and outcomes of acute lung injury. N Engl J Med 2005; 353:1685–93
8. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342: 1301–8
9. Brower RG, Morris A, MacIntyre N, Matthay MA, Hayden D, Thompson T, Clemmer T, Lanken PN, Schoenfeld D; ARDS Clinical Trials Network, National Heart, Lung, and Blood Institute, National Institutes of Health: Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. Crit Care Med 2003; 31:2592–7
10. Gattinoni L, Pelosi P, Crotti S, Valenza F: Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 1995; 151:1807–14
11. Rosenberg AL, Dechert RE, Park PK, Bartlett RH; NIH NHLBI ARDS Network: Review of a large clinical series: Association of cumulative fluid balance on outcome in acute lung injury: A retrospective review of the ARDSnet tidal volume study cohort. J Intensive Care Med 2009; 24:35–46
12. Stewart RM, Park PK, Hunt JP, McIntyre RC Jr, McCarthy J, Zarzabal LA, Michalek JE; National Institutes of Health/National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network: Less is more: Improved outcomes in surgical patients with conservative fluid administration and central venous catheter monitoring. J Am Coll Surg 2009; 208:725–35; discussion 735–7
13. Pavone LA, Albert S, Carney D, Gatto LA, Halter JM, Nieman GF: Injurious mechanical ventilation in the normal lung causes a progressive pathologic change in dynamic alveolar mechanics. Crit Care 2007; 11:R64
14. Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O: What tidal volumes should be used in patients without acute lung injury? Anesthesiology 2007; 106:1226–31
15. Blum JM, Maile M, Park PK, Morris M, Jewell E, Dechert R, Rosenberg AL: A description of intraoperative ventilator management in patients with acute lung injury and the use of lung protective ventilation strategies. Anesthesiology 2011; 115:75–82
16. Bindl L, Dresbach K, Lentze MJ: Incidence of acute respiratory distress syndrome in German children and adolescents: A population-based study. Crit Care Med 2005; 33:209–312
17. Manzano F, Yuste E, Colmenero M, Aranda A, García-Horcajadas A, Rivera R, Fernández-Mondéjar E; Granada Respiratory Failure Study Group: Incidence of acute respiratory distress syndrome and its relation to age. J Crit Care 2005; 20:274–80
18. Flori HR, Glidden DV, Rutherford GW, Matthay MA: Pediatric acute lung injury: Prospective evaluation of risk factors associated with mortality. Am J Respir Crit Care Med 2005; 171:995–1001
19. The Paediatric Study Group of the Australian and New Zealand Intensive Care Society (ANZICS): Acute lung injury in pediatric intensive care in Australia and New Zealand—A prospective, multicentre, observational study. Pediatr Crit Care Med 2007; 8:317–23
20. Krafft P, Fridrich P, Pernerstorfer T, Fitzgerald RD, Koc D, Schneider B, Hammerle AF, Steltzer H: The acute respiratory distress syndrome: Definitions, severity and clinical outcome.

An analysis of 101 clinical investigations. Intensive Care Med 1996; 22:519–29

21. Finigan JH: The coagulation system and pulmonary endothelial function in acute lung injury. Microvasc Res 2009; 77:35–8
22. Walker MG, Yao LJ, Patterson EK, Joseph MG, Cepinskas G, Veldhuizen RA, Lewis JF, Yamashita CM: The effect of tidal volume on systemic inflammation in Acid-induced lung injury. Respiration 2011; 81:333–42
23. Wolthuis EK, Choi G, Dessing MC, Bresser P, Lutter R, Dzoljic M, van der Poll T, Vroom MB, Hollmann M, Schultz MJ: Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury. Anesthesiology 2008; 108:46–54
24. Choi G, Wolthuis EK, Bresser P, Levi M, van der Poll T, Dzoljic M, Vroom MB, Schultz MJ: Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents alveolar coagulation in patients without lung injury. Anesthesiology 2006; 105:689–95
25. Bolin RW, Pierson DJ: Ventilatory management in acute lung injury. Crit Care Clin 1986; 2:585–99
26. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010; 363:1107–16
27. Licker M, de Perrot M, Spiliopoulos A, Robert J, Diaper J, Chevalley C, Tschopp JM: Risk factors for acute lung injury after thoracic surgery for lung cancer. Anesth Analg 2003; 97:1558–65
28. Licker M, Diaper J, Villiger Y, Spiliopoulos A, Licker V, Robert J, Tschopp JM: Impact of intraoperative lung-protective interventions in patients undergoing lung cancer surgery. Crit Care 2009; 13:R41

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Asylum & Main: From Wells to Whoppers



Near the corner of Asylum & Main Streets in Hartford, Connecticut, is a plaque (*left*) marking the site of the dental office where Horace Wells bravely volunteered on December 11, 1844, to undergo dental extraction under nitrous oxide—an *historic first*. Fast-forward to 1895, that same intersection (*right*) marked Hartford's last horse-drawn trolley—an *historic last*. Fast-forward to May of 2013, at the building bearing these very markers, from perhaps the most famously situated Burger King in America, this author placed an order to fill his fat belly—an *historic middle!* (Copyright © the American Society of Anesthesiologists, Inc.)

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