

# Anesthesiology and the Acute Respiratory Distress Syndrome

## *An Ounce of Prevention Is Worth a Pound of Cure*



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**D**URING the 1960s, advances in positive pressure mechanical ventilation led to recognition of a distinct form of respiratory failure precipitated by widespread acute injury to both lungs. Today, clinicians recognize this as the acute respiratory distress syndrome (ARDS), a devastating complication seen after acute illness or injury. Notably, ARDS is also a common cause of postoperative respiratory failure.<sup>1</sup> It is a devastating postoperative complication, with an associated mortality rate of up to 45%.<sup>1</sup> Beyond mortality, ARDS imparts a substantial burden on healthcare resource utilization. Furthermore, survivors frequently experience long-term physical impairments as well.<sup>2</sup> As a remarkably underappreciated complication of surgery, it is not surprising that research that is specifically focused on ARDS in the surgical setting has been sparse. Moreover, the limited work performed in this regard has primarily focused on populations undergoing high-risk cardiothoracic and vascular surgery. In this issue of *Anesthesiology*, Dr. Blum *et al.*<sup>3</sup> aim to enhance our understanding of this critical illness syndrome by focusing on an understudied cohort, namely those patients undergoing low-risk surgery.



***“... Dr. Blum et al. have provided important new insights into the incidence and risk factors for postoperative ARDS among low-risk surgical populations.”***

Despite promising preclinical data for a variety of treatments for ARDS, translation to clinical benefit has been frustratingly elusive. Presently, we are mostly left with the avoidance of additional lung injury *via* protective ventilator settings and a conservative approach to fluid management as supportive therapies.<sup>4,5</sup> In light of this fact, interest in ARDS prevention is gaining steam. Indeed, prevention of ARDS was recently identified as a key priority for the National Heart Lung and Blood Institute. This new emphasis is manifested in recent ARDS working group publications and in a change of emphasis in the current renewal of the ARDS network. Specifically, this network will now be known as the National Heart Lung and Blood Institute Clinical Trials Network for the Prevention and Treatment of Acute Lung Injury (PETAL Network - NHLBI-HR-14-03).<sup>6</sup> Importantly, however, prevention strategies for ARDS are similarly limited at present. With the exception of restrictive transfusion practices and the avoidance of injurious ventilator settings,<sup>7</sup> no effective ARDS prevention agents currently exist. Indeed, the first major ARDS prevention trial, evaluating the efficacy of aspirin, has just recently been initiated.<sup>8</sup>

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◆ This Editorial View accompanies the following article: Blum JM, Stentz MJ, Dechert R, Jewell E, Engoren M, Rosenberg AL, Park PK: Preoperative and intraoperative predictors of postoperative acute respiratory distress syndrome in a general surgical population. *ANESTHESIOLOGY* 2013; 118:19-29.

Historically, a critical barrier to progress in prevention of ARDS has been the lack of effective prediction models that can reliably identify populations with high risk for this serious complication. Without early and effective risk stratification, any potentially beneficial prevention strategies will be delivered either too late or to the wrong population. Furthermore, with an estimated incidence of 3% in high-risk surgical populations, testing prevention strategies in unselected surgical populations is inefficient, expensive, and potentially unsafe.<sup>1</sup> To this end, identification of important risk factors for ARDS is the necessary first step in making progress toward effective prevention. Although recent efforts have begun to address this important knowledge gap, to date, work has primarily focused on medical patients or on those undergoing surgical procedures that are already understood to place the patient at risk.<sup>9,10</sup> Examples include those undergoing cardiac, noncardiac thoracic, and vascular surgery. In contrast, the incidence, risk factors, and outcomes of patients with ARDS have been largely ignored in lower-risk surgical populations. The work of Dr. Blum *et al.*<sup>3</sup> aims to address this important knowledge gap. Specifically, the objectives of this investigation included determination of: (1) the incidence and preoperative risk factors for ARDS in patients undergoing low-risk surgery and (2) the intraoperative variables associated with increased risk of this life-threatening respiratory complication.

To identify the desired low-risk surgical population, the investigators evaluated all anesthetics administered at a single major academic medical center and cross-referenced this list with a second prospectively collected database containing all adult critical care patients receiving mechanical ventilation, who were screened for entry into ARDS-related studies. Patients undergoing high-risk procedures such as cardiac, thoracic, transplant, trauma, and vascular surgery were specifically excluded. Using this large database-driven retrospective cohort, the investigators were able to determine the incidence of ARDS in this population. From within this large cohort, a nested case-control study was then used to facilitate the targeted identification of intraoperative risk factors that may contribute to the development of postoperative ARDS. Confounding effects from baseline demographic and clinical predictors of ARDS were largely mitigated by matching each ARDS case to four control subjects, based upon their preoperative likelihood of developing ARDS (American Society of Anesthesiologists physical status 3 or higher, emergent procedure, asthma, renal failure, chronic obstructive pulmonary disease, male sex, and the number of anesthetics administered during the admission).

A number of important findings from this investigation deserve mention. First and foremost is the remarkably low incidence rate for ARDS. Indeed, the incidence of 0.2% noted by Blum *et al.*<sup>10</sup> contrasts starkly with previously reported incidence rates ranging as high as 23% for specific high-risk vascular surgery populations. However, previous

studies have repeatedly reinforced a key role of the specific surgical procedure in determining risk for postoperative ARDS. Indeed, multiple previous investigations have also identified widely disparate rates of ARDS, with the variability largely depending on the nature of the surgical procedure.<sup>1,9,10</sup> Therefore, it is not entirely surprising that such a low rate was encountered in this study, given the low-risk nature of the surgical population evaluated. In contrast, the impact of ARDS on patient-important outcomes remained substantial despite the low-risk nature of the surgical procedures included. As the investigators correctly point out, an ARDS-associated mortality rate of 27% is quite consistent with the available literature and is entirely unacceptable in a low-risk surgical population. Indeed, it seems the ARDS-related risk of death is largely independent of the population's baseline surgery-related risk.

Additional key findings of Dr. Blum's work include the identified risk factors for postoperative ARDS. The associations between American Society of Anesthesiologists physical status, emergent surgery, chronic obstructive lung disease, increased intraoperative airway pressures, high fraction of inspired oxygen, and aggressive fluid and transfusion therapies with postoperative ARDS seem robust as they are consistent with multiple previous reports in high-risk surgical populations. Although the association between the number of anesthetics administered during an admission and rate of ARDS is less well described, there would seem to be biologic plausibility. Indeed, the need for multiple anesthetic encounters during the same admission would seem to suggest either the staging of a complex surgical procedure/patient or the presence of complications arising from the index surgical procedure. As multiple reports suggest that the occurrence of a postoperative complication begets additional complications, we might expect this to hold true for ARDS as well. In contrast, the causal links associating male sex and renal failure with postoperative ARDS are less well described and without further validation should be interpreted with caution.

Of perhaps greatest interest to the readers of this journal are the potentially modifiable risk factors that have been identified from within the operating room environment. Indeed, the temporal proximity of these variables with the great preponderance of ARDS cases (consistent with prior reports, the majority of cases in the current investigation occurred within the first 24–48 h of the surgical procedure) suggests that intraoperative exposures and patient responses may indeed play key roles in ARDS pathogenesis. However, although the potential for mitigating risk for ARDS by altering anesthetic management is enticing, we must proceed with caution as important questions remain. In particular, this observational study (indeed all observational studies) cannot reliably differentiate cause–effect relationships from simple associations. For example, it is not clear whether the high ventilator driving pressures encountered during the operative course truly lead to increased risk for ARDS. These may simply indicate the presence of prevalent lung/

chest-wall disease in these patients. The lack of an association between tidal volume and development of ARDS may suggest the latter. This dissonance suggests that lowering tidal volume, although important, is not always enough and that additional measures to reduce the ventilator driving pressure may be necessary in certain patients. Such measures could include raising the level of positive end-expiratory pressure to improve lung recruitment or ensuring adequate muscle relaxation.<sup>11,12</sup> Similarly, though prolonged exposure to high levels of oxygen may clearly result in lung injury, it is less certain whether relatively brief exposure to high  $\text{FiO}_2$  (as would be expected in this low-risk surgical cohort) might have a similar effect. Perhaps more likely, the presence of a high  $\text{FiO}_2$  may again simply identify those with prevalent lung disease, or alternatively, the early development of lung injury. Regardless, in light of the well-documented potential for cause–effect relationships, particularly for transfusion therapies and injurious ventilator settings, it would clearly seem prudent to limit tidal volume/peak airway pressures and to avoid overly aggressive transfusion strategies whenever possible.

Overall, the findings of this study are both novel and significant. However, though the clearly defined hypotheses, large sample size (more than 50,000 patients), and detailed statistical plan are clear strengths of the current investigation, several limitations should be noted. In addition to the inability to determine cause–effect relationships, it must be recognized that the study population arose from a single academic medical center. As a result, the external validity and generalizability of the findings remain unclear. In addition, as with any large database study, data integrity and validity were largely untested. Therefore, concerns relating to both false-positive (type I error) and false negative (type II error) associations remain. Perhaps the lack of an association between alcohol abuse (and perhaps smoking) with risk for ARDS, which has been described in multiple prior studies, is partially explained by this concern.<sup>10</sup> In addition, a database-driven design precludes an evaluation of potentially important variables that are simply not in the database. In the current case, missing variables that have previously been associated with postoperative ARDS included elements from both the preoperative domain (*e.g.*, gastroesophageal reflux disease, sepsis, aspiration, pancreatitis, immunosuppression) and the intraoperative course (*e.g.*, duration of the surgical procedure and hemodynamic status). The lack of such variables results in a less robust understanding of who is at risk for postoperative ARDS. In addition, these missing data also lead to potentially important unmeasured confounding. Finally, the definition for ARDS in this investigation required endotracheal intubation. Although consistent with the definition of ARDS used in multiple other investigations, less-severe cases could well have been missed. As a result, the true incidence of ARDS in patients undergoing low-risk surgery may be somewhat greater than reported in this investigation.

Despite the abovementioned limitations, Dr. Blum *et al.*<sup>3</sup> have provided important new insights into the incidence and risk factors for postoperative ARDS among low-risk surgical populations. Although the incidence seems low, the impact of ARDS on patient-important outcomes remains substantial. As we work to make progress on the prevention of postoperative ARDS, our ability to identify surgical populations who are at high risk is an essential first step. To this end, the current investigation has clearly advanced our knowledge. In addition to validating the associations identified in the current investigation, future studies must work to enhance our understanding of true nature of these associations. If causal relationships are confirmed, the potential for mitigating the onset and severity of postoperative ARDS by the way we deliver care in the operating room may well exist. If true, how important this would be. After all, an ounce of prevention is worth a pound of cure!!

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