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In Reply:—We thank Dr. Mulroy for his comments on voiding requirement in outpatients receiving neuraxial blockade with short-acting local anesthetic. We would like to take the opportunity to clarify some issues raised by Dr. Mulroy.

In our review,[1] we identified several risk factors for postoperative urinary retention (POUR), such as type and duration of surgery, patient comorbidities, intraoperative fluid management, and choice of anesthetic and analgesic technique.

In the setting of ambulatory surgery, we proposed an algorithm based in part on two previous studies by Pavlin *et al.*[2,3] In the first study, patients were stratified before surgery in high and low risk for POUR. Patients who had a past history of urinary retention and those who underwent anorectal and inguinal hernia repair surgery were considered at high risk, even if they did not receive either spinal or epidural anesthesia. In the second study,[3] 27% of the patients who received neuraxial anesthesia with local anesthetic (bupivacaine or lidocaine ± epinephrine) were unable to void and had a bladder volume greater than 600 ml, thus requiring in-and-out bladder catheterization. These patients were identified by Pavlin *et al.* as high risk only because they received neuraxial anesthesia. However, in our opinion, the high incidence of POUR in this group was not caused by the use of spinal–epidural anesthesia *per se*, but by the use of long-acting local anesthetics. Mulroy *et al.*,[4] in contrast, studied 46 patients without risk factors for POUR who received spinal or epidural anesthesia with short-acting local anesthetic with or without intrathecal fentanyl and who were discharged without voiding. None of them returned to the hospital because of POUR.

The aim of our review was to bring to the attention of anesthesiologists the perioperative risk factors for POUR, and propose an algorithm on how to manage urinary retention judiciously. We agree with Dr. Mulroy that in outpatients with no risk factors for POUR, neuraxial anesthesia with short-acting local anesthetic does not increase the risk of POUR, and patients can be discharged home without voiding. However, in patients with preoperative risk factors for POUR, neuraxial anesthesia with short-acting local anesthetic may or may not further increase the risk, but the availability of a perioperative algorithm that includes the use of a bladder scan could facilitate the management of this potential complication.

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High Positive End-expiratory Pressure and Mortality in Acute Respiratory Distress Syndrome

To the Editor:—In acute lung injury and acute respiratory distress syndrome (ARDS), the aim of positive end-expiratory pressure (PEEP) is to recruit lung tissue preventing the cyclic opening and closing of alveoli (atelectrauma).[1] However, PEEP is associated to deleterious pulmonary (overdistension of healthy tissue) and hemodynamic (decreased venous return, abnormalities in organ blood flow) effects.[2–4] In recent years, several studies have attempted to answer the question of which PEEP should be used in acute lung injury and ARDS. Two strategies may be used: the setting of a "low" PEEP to minimize its secondary effects or a "high" PEEP to maximize lung recruitment and gas exchange (open lung strategy). In their recent meta-analysis, Phoenix *et al.*[5] observed that, in ARDS patients, the use of a high-PEEP strategy showed a trend toward improved mortality and increased risk of barotrauma, although these changes were not statistically significant. However, the authors stated that "the benefits [of this strategy] far outweigh potential risks" and considered that "current evidence supports the use of high PEEP in unselected groups of patients."

A major limitation in these studies is the lack of definition of high PEEP. Protocols include two strategies in which one of the groups is randomly assigned to receive a higher level of PEEP than the other. The selection of the PEEP level is rather arbitrary, based on oxygenation criteria, and always limiting the plateau pressure. The PEEP is never individualized according to the primary cause (pulmonary *vs.* extrapulmonary) or severity of ARDS. Results are not conclusive, because every group includes patients who require different levels of PEEP. Therefore, the potential benefits of a specific strategy in some of the patients in a group are likely neutralized by the deleterious effects on the rest of the patients. Another reason that may explain the lack of conclusive results is the limitation of the plateau pressure in all patients, which plays a major role in outcome and may be more important that the level of PEEP in unselected cases.

The results from the meta-analysis are in accord with recent literature questioning the decrease in mortality in ARDS in the past decade despite the implementation of new ventilatory strategies.[6–8] In the ARDSNet trial,[9] a significant reduction in mortality was observed when a "protective strategy," based on a low tidal volume (6 ml/kg), was used. But we may speculate that patients were actually being protected from an "aggressive strategy" (tidal volume 12 ml/kg in the control arm). It is likely that the application of a high PEEP in the initial phase of severe ARDS, with an expected important lung edema and inflammation, is justified.[10] Even accepting this approach, it remains unanswered for how long the PEEP should be "high." The lack of clear benefits in unselected patients is probably related to the absence of objective tests that help in the individual titration of the ventilatory parameters. Several techniques have been proposed, such as the plotting of pressure–volume curves,[11] the stress index[12] (actually a sort of dynamic pressure–volume curve), or the electrical impedance tomography.[13] Interestingly, in the three smaller studies included in the meta-analysis by Phoenix *et al.*[5] but finally excluded for the conclusions, PEEP was set according to the pressure–volume curve. Of note is the apparent major benefit observed with a high PEEP level in these studies. Until recruitment/derecruitment and hyperinflation are not estimated repeatedly in individual ARDS patients as their lung injury

evolves, it is unlikely that any attempt to demonstrate the superiority of a ventilatory strategy will be conclusive.

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In Reply:—Thank you for giving us the opportunity to respond to the communication by Dr. David Pestaña. The author is correct in his assertion that most of the studies do not define the terms *high positive end-expiratory pressure (PEEP)* and *low PEEP* and that the appropriate level of PEEP has been selected on the basis of oxygenation and peak/plateau airway pressures.[1–3] This reflects the practical difficulties inherent in recruiting large numbers of patients into clinical trials using highly individualized criteria. We are therefore left with the mean values recoded in each of the groups to infer the threshold values for "low" and "high" PEEP. Nevertheless, the underlying physiologic principles are clear and suggest that there are several biologic benefits associated with selecting PEEP levels between 10 and 15 cm H_2O in patients with severe acute lung injury. This is particularly so during the early stages of the illness, when lung edema is maximal and therefore the tendency for cyclical opening and collapse of alveolar units is maximal.[1–5] The author is also correct in stating that the most appropriate level of PEEP in a given patient can only be determined through an individualized titration protocol. He raises a pertinent point in his final statement that "it is unlikely that any attempt to demonstrate the superiority of a ventilatory strategy will be conclusive." We agree entirely and would like to pose the question of whether the current emphasis on the need to demonstrate significant improvements in final outcome–based endpoints (mortality, duration of stay, duration of mechanical ventilation, and so forth) is appropriate for evaluating new ventilation strategies.

Ventilation is a supportive measure needed in the management of other systemic illnesses such as sepsis, acute lung injury/acute respiratory distress syndrome, systemic inflammatory response syndrome, and heart failure. Clinical outcome in such patients is usually a manifestation of the underlying disease process itself or the "mediator variables." Ventilation, in this context, is best seen as a "moderator variable" that alters the quantitative relation between disease severity and its consequence (mortality and or morbidity). Improvements in ventilation strategies can, therefore, have only a modest impact on disease specific mortality. As iatrogenic contributions to mortality (such as excess sedation, barotrauma/volutrauma, and ventilator-induced lung injury) are recognized and rectified, it becomes inevitable that further improvements in ventilator technology will require an unrealistic sample size to demonstrate mortality/morbidity benefits based on the basic principles of diminishing returns.[5] Such large numbers cannot be recruited within a geographically, culturally, and economically homogeneous area or during a reasonable time period during which clinical practices remain comparable across several other domains. More importantly, it is well recognized that interactions between organ systems in humans are nonlinear, and the importance of such nonlinearity in critical illness was highlighted elegantly by Buchman[6] and Rixen *et al.*[7] If we agree on the most fundamental premise that the initial manifestations and subsequent development of a disease state are governed by nonlinear interactions between the severity of the initial insult (the mediator variables), host's physiologic responses, and other moderator variables (such as ventilation, secondary infections, iatrogenic complications, and nutritional status), it follows that each patient would follow a unique trajectory as dictated by nonlinear dynamics. In such nonlinear systems, the final clinical outcome (survival, death, or prolonged morbidity) is unpredictable and is sensitively dependant on the initial conditions (the mediator variables) and subsequent modulator variables. It does not follow simple rules based on linear assumptions. That is, a "small change" in one of the moderator variable does not always lead to a "small change" in the final outcome. Such "unpredictable" events occurring (in the control or treatment arms) in clinical trials involving moderator variables, with a relatively modest influence on the overall disease process, will necessarily lead to conclusions that are difficult to reproduce and at times erroneous. Therefore, the current emphasis placed on clinical outcome alone reflects a mind-set (promoted by the business world) that is rooted in cost–benefit analysis and aims to identify and support only those interventions with a relatively large effect size. This approach, if adopted blindly and dogmatically, is likely to lead to the abandonment of several interventions that may be beneficial to individual patients.

Estimating the qualitative and quantitative improvements to patient care that can be achieved by refining moderator variables (such as ventilation), in our view, requires the adoption of more dynamic models as suggested by Dr. Pestaña, rather than the final clinical outcome alone.