Sustained Inflation of Infant Lungs: From Bench to Bedside and Back Again

Moments after birth, the newborn infant must transition from an aqueous environment with placental support of gas exchange to air breathing. To do so, the newborn must rapidly aerate his or her fluid-filled lungs, establish adequate FRC, and dramatically increase pulmonary blood flow. Vigorous full-term infants typically accomplish this remarkable transition quickly and effectively, but extremely low-gestational-age neonates may fail to generate sufficient inspiratory pressure to reach the critical opening pressure of fluid-filled airspaces and move fluid through very small airways (1). Their excessively compliant chest wall will fail to sustain any FRC that may have been achieved—a problem that is compounded by a paucity of surfactant. Cesarean delivery is common and is well known to result in a greater amount of residual lung fluid. Thus, subsequent tidal breathing, both spontaneous and delivered by positive pressure ventilation, may occur in lungs that are only partially aerated, causing volutrauma even with a normal physiologic V_T.

Volutrauma can occur within minutes of birth in premature animals (2), which suggests that achieving an even distribution of V_T in a fully aerated lung from the very onset of tidal breathing might be important. Sustained inflation (SI), a maneuver that delivers inflation pressure between 15 and 30 cm H_2O for up to 15 seconds, has become a widespread practice, especially in Europe. There is a sound rationale for this concept, given the much higher viscosity of lung fluid compared with air and the resulting much longer time constant required to move fluid through very small airways. Preclinical studies have demonstrated that SI achieves uniform lung aeration more rapidly than tidal ventilation with positive end-expiratory pressure (PEEP) (3). A series of preclinical studies showed that SI can be effectively delivered in animals via an endotracheal tube (4, 5). However, not all such studies showed benefit (6).

Early clinical trial evidence suggested that SI may reduce the need for mechanical ventilation (7). A more recent systematic review found less support for SI (8). The largest and most recent clinical trial, dubbed the SAIL (Sustained Aeration of Infant Lungs) trial, was terminated before it reached its target sample size of 600 because of increased early mortality in the intervention group (9). Although there was no difference in overall mortality, it was evident after enrollment of over two-thirds of the target sample population that there was a negligible chance of showing any benefit. That study exclusively enrolled the most immature infants at 22–26 weeks of gestation, and perhaps illustrates the pitfalls of extrapolating findings from more mature infants to those at the borderline of viability.

In this context, the elegant study by Tingay and colleagues published in this issue of the *Journal* (pp. 608–616) offers valuable insights into the increasingly controversial issue of how best to facilitate lung aeration in preterm infants (10). Building on a series of investigations of lung-aeration strategies in a preterm lamb model, the authors performed a comprehensive evaluation of the effects of three different methods of achieving lung aeration at birth. For this purpose, they examined regional patterns of lung inflation and injury using electrical impedance tomography (EIT), gas exchange, lung mechanics, lung histology, and mRNA expression of six early biomarkers of lung injury. The approach that strives to achieve lung aeration gradually with positive pressure inflations superimposed on escalating and de-escalating PEEP (dynamic PEEP) resulted in more uniform lung aeration, better dynamic compliance, and oxygenation than SI or no recruitment maneuver. Patterns of lung injury were consistent with the spatiotemporal patterns visualized by EIT. The SI lambs showed upregulation of lung injury marker genes in the dependent regions of the lungs. The authors speculate that the protective effects of the dynamic PEEP approach may be due in part to the lower initial V_T delivery that results from limiting the peak inspiratory pressure while escalating PEEP at a time when the lung is only partially aerated.

The strengths of this study include the thoroughly worked-out approach to exploring regional volume-related lung injury patterns, the seasoned investigative team, management that closely mimics clinical reality (antenatal steroids and postnatal surfactant), adequate statistical power, and comprehensive assessment of the distribution of ventilation, lung mechanics, and a variety of measures of lung injury. Importantly, the study challenges the widely held dogma that SI is the best way to aerate immature lungs, and provides further evidence for an alternative strategy that may promote uniform aeration in a less aggressive manner.

The study's limitations include the fact that the intervention was delivered via a cuffed endotracheal tube and spontaneous breathing was suppressed. Emerging evidence indicates that in the absence of spontaneous breathing, the glottis is closed and pressure that is delivered noninvasively may not be transmitted to the lower airway effectively (11, 12). This may have a bearing on the generalizability of the findings to the clinical situation, where in the initial attempt to achieve aeration, ventilation is typically delivered via a face mask. Although it has some technical limitations (13), EIT is increasingly becoming accepted as the only practical method for assessing regional ventilation and aeration patterns, which is an important assessment in view of the mounting evidence that initial lung aeration is quite nonuniform. Previous studies indicated that lambs require higher inflation pressures and longer inflation times for SI than human infants; therefore, the specific pressures and duration of SI used in this study are not directly translatable to human subjects. Similarly, most clinicians would be uncomfortable with the levels of PEEP used here. Although they were based on previous studies that suggested that these are the optimal settings, it is possible that the SI duration and pressure were overly aggressive. Finally, the authors did not evaluate possible effects of this

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maneuver on cardiac output, pulmonary blood flow, or cerebral hemodynamics—issues of obvious relevance in future clinical trials.

One should always exercise caution when extrapolating data from animal research to the clinical setting. Indeed, the story of the journey of SI from animal research to widespread clinical use, and now perhaps a pullback after the report of sobering data from a major clinical trial, is a case in point. Nonetheless, the findings of the present study are important and clearly suggest the need for clinical investigations of different approaches to lung recruitment during stabilization of low-gestational-age neonates, with an emphasis on dynamic PEEP strategies that transiently use levels that may be well beyond the comfort level of many practitioners. ■

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Martin Keszler, M.D.
Alpert Medical School of Brown University
Providence, Rhode Island
and
Women and Infants Hospital of Rhode Island
Providence, Rhode Island

ORCID ID: 0000-0002-9964-664X (M.K.).

References

1. te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth. *J Pediatr* 2008;152:607–611.
2. Björklund LJ, Ingimarsson J, Curstedt T, John J, Robertson B, Werner O, *et al*. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Pediatr Res* 1997;42: 348–355.
3. te Pas AB, Siew M, Wallace MJ, Kitchen MJ, Fouras A, Lewis RA, *et al*. Establishing functional residual capacity at birth: the effect of sustained inflation and positive end-expiratory pressure in a preterm rabbit model. *Pediatr Res* 2009;65:537–541.
4. Sobotka KS, Hooper SB, Allison BJ, Te Pas AB, Davis PG, Morley CJ, *et al*. An initial sustained inflation improves the respiratory and cardiovascular transition at birth in preterm lambs. *Pediatr Res* 2011; 70:56–60.
5. Polglase GR, Tingay DG, Bhatia R, Berry CA, Kopotic RJ, Kopotic CP, *et al*. Pressure- versus volume-limited sustained inflations at resuscitation of premature newborn lambs. *BMC Pediatr* 2014; 14:43.
6. Hillman NH, Kemp MW, Miura Y, Kallapur SG, Jobe AH. Sustained inflation at birth did not alter lung injury from mechanical ventilation in surfactant-treated fetal lambs. *PLoS One* 2014;9:e113473.
7. Schmölzer GM, Kumar M, Aziz K, Pichler G, O'Reilly M, Lista G, *et al*. Sustained inflation versus positive pressure ventilation at birth: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F361–F368.
8. Bruschettini M, O'Donnell CP, Davis PG, Morley CJ, Moja L, Zappettini S, *et al*. Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes. *Cochrane Database Syst Rev* 2017;7:CD004953.
9. Kirpalani H, Ratcliffe SJ, Keszler M, Davis PG, Foglia EE, Te Pas A, *et al*. Effect of sustained inflations vs intermittent positive pressure ventilation on bronchopulmonary dysplasia or death among extremely preterm infants: the SAIL randomized clinical trial. *JAMA* 2019;321: 1165–1175.
10. Tingay DG, Pereira-Fantini PM, Oakley R, McCall KE, Perkins EJ, Miedema M, *et al*. Gradual aeration at birth is more lung protective than a sustained inflation in preterm lambs. *Am J Respir Crit Care Med* 2019;200:608–616.
11. Crawshaw JR, Kitchen MJ, Binder-Heschl C, Thio M, Wallace MJ, Kerr LT, *et al*. Laryngeal closure impedes non-invasive ventilation at birth. *Arch Dis Child Fetal Neonatal Ed* 2018;103: F112–F119.
12. Schmölzer GM, Dawson JA, Kamlin CO, O'Donnell CP, Morley CJ, Davis PG. Airway obstruction and gas leak during mask ventilation of preterm infants in the delivery room. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F254–F257.

Involvement of PFKFB3 in Pulmonary Arterial Hypertension Pathogenesis

Is It All about Glycolysis?

In mammals, cell proliferation is required for several physiological processes, including embryogenesis, growth, and proper function of several adult tissues, but it is also central to disease development, including tumorigenesis (1) and vascular remodeling (2). Proliferating cells require nutrients, energy, and biosynthetic activity to duplicate proteins, lipids, and nucleic acids during each passage through the cell cycle (3). It is therefore not surprising that metabolic activities in proliferating cells are fundamentally different from those in nonproliferating cells and support a platform for biosynthesis. In the 1920s, Otto Warburg described for the first time that rapidly proliferating ascites tumor cells consume glucose at a surprisingly high rate compared with normal cells and secrete most of the glucose-derived carbon as lactate rather than oxidizing it completely. The high glycolytic rate provides several advantages for proliferating cells: it allows cells to use the most abundant extracellular nutrient (i.e., glucose) to produce glucose-derived molecules necessary to biosynthetic pathways. The rate of glycolytic flux is controlled at different levels and by different mechanisms, but the first rate-limiting step is the conversion of fructose-6-phosphate (F6P) to fructose-1,6-bisphosphate (F1,6P2) by 6-phosphofructo-1-kinase (PFK-1). The intracellular allosteric regulator fructose

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