10. Yu K, Qiu G, Chan KH, Lam KH, Kurmi OP, Bennett DA, *et al.* Association of solid fuel use with risk of cardiovascular and all-cause mortality in rural China. *JAMA* 2018;319:1351–1361.
11. Alexander D, Larson T, Bolton S, Vedal S. Systolic blood pressure changes in indigenous Bolivian women associated with an improved cookstove intervention. *Air Qual Atmos Health* 2014;8:47–53.
12. Alexander D, Northcross A, Wilson N, Dutta A, Pandya R, Ibigbami T, *et al.* Randomized controlled ethanol cookstove intervention and blood pressure in pregnant Nigerian women. *Am J Respir Crit Care Med* 2017;195:1629–1639.
13. Checkley W, Williams KN, Kephart JL, Fandiño-Del-Rio M, Steenland NK, Gonzales GF, *et al.*; CHAP Trial Investigators. Effects of a household air pollution intervention with liquefied petroleum gas on cardiopulmonary outcomes in Peru: a randomized controlled trial. *Am J Respir Crit Care Med* 2021;203:1386–1397.
14. Smith KR, McCracken JP, Weber MW, Hubbard A, Jenny A, Thompson LM, *et al.* Effect of reduction in household air pollution on childhood pneumonia in Guatemala (RESPIRE): a randomised controlled trial. *Lancet* 2011;378:1717–1726.
15. Lee AG, Kaali S, Quinn A, Delimini R, Burkart K, Opoku-Mensah J, *et al.* Prenatal household air pollution is associated with impaired infant lung function with sex-specific effects: evidence from GRAPHS, a cluster randomized cookstove intervention trial. *Am J Respir Crit Care Med* 2019;199:738–746.

Lung Ultrasound in Early Preterm Life: A Window into the Future?

Because of the need for the lung to engage in gas exchange before alveolarization, preterm birth is fundamentally a developmental respiratory problem that often results in surfactant-deficient respiratory distress syndrome (RDS) and the need for assisted respiratory support (1). For many preterm infants, the interaction between abnormal lung development, altered lung mechanics, complications of respiratory support, and secondary factors creates a cascade of injury and inflammatory events, causing chronic lung disease, specifically bronchopulmonary dysplasia (BPD) (1). Reducing the burden of chronic lung disease has been hampered by difficulties in accurately identifying the lung conditions in early preterm life that predispose to later BPD. The study by Loi and colleagues in this issue of the *Journal* (pp. 1398–1409), verifying the potential of ultrasound of the lung (LUSS) to assess lung aeration and identify infants likely to progress to BPD, makes an important contribution to addressing this challenge (2).

In their multicenter, prospective, observational study, Loi and colleagues describe the relationship between standardized LUSS performed on Days 1, 7, 14, and 28 after birth with concurrent blood gas and clinical respiratory status in 147 preterm infants born at less than 31 weeks of gestation (2). Ultrasound interaction with the highly reflective pleura produces different artifact patterns that correlate with pulmonary aeration (3). The authors used a semiquantitative scoring system they had previously shown to predict short-term outcomes, including surfactant administration and response and noninvasive ventilation failure (2–5). Each lung was divided into three regions (upper anterior, lower anterior, and lateral), and scores were assigned on the basis of the observed ultrasound artifact pattern. Higher scores indicate worsening degrees of aeration. This LUSS score correlated moderately well with objective indices of impaired oxygenation and hypercapnia, and with subjective clinical assessment of RDS. The authors have highlighted key advantages of LUSS over other imaging modalities for this population. LUSS does not expose the preterm infant to ionizing radiation or require transfer from the neonatal ICU. Bedside ultrasound is widely available and accepted in neonatology. LUSS is easy to learn, and exhibits a high degree of interobserver agreement (3). The authors report that accurate image acquisition took an average of 3 minutes, although whether this can be replicated in less skilled hands requires confirmation.

BPD was diagnosed in 50% of infants in the study at 36 weeks corrected gestation. The most interesting finding of the study was the association between Days 7 and 14 gestational age–adjusted LUSS score and later BPD status. The ability of LUSS to predict BPD (71% sensitivity and 74% specificity at Day 7) is similar to existing BPD prediction tools (6–8). There is a strong rationale to focus on prediction in the first 2 weeks after preterm birth. In this period, the underdeveloped preterm lung with RDS is most at risk of injury (1, 9). It is increasingly apparent that the early events traditionally associated with BPD, such as oxygen exposure and barotrauma from invasive ventilation, are only part of the developmental, inflammatory, biotrauma, and mechanotrauma puzzle leading to BPD (10). This is also the period with the greatest potential to modulate BPD risk using interventions that blunt the early injury/inflammation cascade before secondary chronic injury occurs. The promising findings from Loi and colleagues' study suggest that serial LUSS offers a powerful functional tool for temporal characterization of early preterm lung disease.

Prediction is not prevention, and an ideal predictive tool should also guide intervention. There are many respiratory therapies available for RDS, but there is little evidence of difference between them with regard to BPD outcomes (1). The art of lung protection requires knowing therapy that may benefit a specific infant. As RDS is expressed differently within the lung and changes over time, optimizing respiratory therapies requires functional dynamic tools. Obtaining the fine balance between lung protection and injury has been hampered by crude tools, such as chest radiography, oxygenation, and clinical assessment. LUSS and electrical impedance tomography (EIT) are emerging dynamic, repeatable bedside methods of assessing lung function at a regional level that may offer the precision currently lacking (11, 12). As a research tool, EIT can differentiate ventilation homogeneity patterns related to molecular lung injury from respiratory interventions in preclinical

D.G.T. is supported by a National Health and Medical Research Council Clinical Career Development Fellowship (grant 1053889). D.G.T. and A.S. are supported by the Victorian Government Operational Infrastructure Support Program (Melbourne, Australia).

Originally Published in Press as DOI: 10.1164/rccm.202101-0091ED on February 8, 2021

models of RDS, and it can also predict later BPD status in preterm infants (10, 12, 13). Unlike EIT, LUSS has the advantage of being clinically available now. Hopefully, the authors will next address whether LUSS scores of regional aeration states have the precision and repeatability to allow clinicians to meaningfully individualize respiratory therapies.

The trajectory from RDS to chronic lung disease is an inherent weakness of any BPD predictive tool. RDS is a developmental disease of exclusion, as there are no currently available techniques to accurately diagnosis the degree of surfactant deficiency. Furthermore, there is considerable controversy about how best to characterize and diagnose BPD (9); definitions based on oxygen or respiratory support requirements have both been used (6, 8). Arguably, any definition of BPD will not truly reflect the trajectory of lung aging, alveolarization, and function after preterm birth or the interplay of initial inflammation, oxygen, and mechanotrauma events influencing it (14). The unfortunate reality is that BPD status is also not the endpoint for chronic lung disease of prematurity. No definition of BPD describes the lung function trajectory toward chronic obstructive pulmonary disease in early adulthood seen in many preterm survivors (15). Therefore, although the cohort without BPD may not have the short-term diagnosis of BPD, they may still be at risk of the more meaningful long-term respiratory complications of preterm birth.

Exactly what BPD is continues to challenge neonatologists. Could LUSS contribute to tracking the trajectory of abnormal lung development associated with prematurity? There is no doubt that LUSS can offer a window into the future, but the more important question is determining which future to look toward. The abnormal trajectory of lung development in preterm survivors likely results from mechanisms that differ from the traditional associations of BPD. Our conclusions are that a research agenda to avoid the outcome of early chronic lung disease is more important than new research that focuses on the early effects of BPD, such as prolonged oxygen use or respiratory support. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

David G. Tingay, M.D., Ph.D.
Neonatal Research
Murdoch Children's Research Institute
Parkville, Australia

Neonatology
The Royal Children's Hospital
Parkville, Australia

and

Department of Paediatrics
University of Melbourne
Melbourne, Australia

Arun Sett, M.B. B.S.
Neonatal Research
Murdoch Children's Research Institute
Parkville, Australia

Alan H. Jobe, M.D., Ph.D.,
Neonatology/Pulmonary Biology
Cincinnati Children's Hospital
Cincinnati, Ohio

and

University of Cincinnati School of Medicine
Cincinnati, Ohio

References

1. Thébaud B, Goss KN, Laughon M, Whitsett JA, Abman SH, Steinhorn RH, *et al.* Bronchopulmonary dysplasia. *Nat Rev Dis Primers* 2019;5:78.
2. Loi B, Vigo G, Baraldi E, Raimondi F, Carnielli VP, Mosca F, *et al.*; LUSTRE Study Group. Lung ultrasound to monitor extremely preterm infants and predict bronchopulmonary dysplasia: a multicenter longitudinal cohort study. *Am J Respir Crit Care Med* 2021;203: 1398–1409.
3. Singh Y, Tissot C, Fraga MV, Yousef N, Cortes RG, Lopez J, *et al.* International evidence-based guidelines on point of care ultrasound (POCUS) for critically ill neonates and children issued by the POCUS working group of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). *Crit Care* 2020;24:65.
4. Brat R, Yousef N, Klifa R, Reynaud S, Shankar Aguilera S, De Luca D. Lung ultrasonography score to evaluate oxygenation and surfactant need in neonates treated with continuous positive airway pressure. *JAMA Pediatr* 2015;169:e151797.
5. Raimondi F, Migliaro F, Sodano A, Ferrara T, Lama S, Vallone G, *et al.* Use of neonatal chest ultrasound to predict noninvasive ventilation failure. *Pediatrics* 2014;134:e1089–e1094.
6. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, *et al.* The diagnosis of bronchopulmonary dysplasia in very preterm infants: an evidence-based approach. *Am J Respir Crit Care Med* 2019;200:751–759.
7. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, *et al.*; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. *Am J Respir Crit Care Med* 2011;183:1715–1722.
8. Svedenkrans J, Stoecklin B, Jones JG, Doherty DA, Pillow JJ. Physiology and predictors of impaired gas exchange in infants with bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2019;200:471–480.
9. Jobe AH, Steinhorn R. Can we define bronchopulmonary dysplasia? *J Pediatr* 2017;188:19–23.
10. Pereira-Fantini PM, Pang B, Byars SG, Oakley RB, Perkins EJ, Dargaville PA, *et al.* Preterm lung exhibits distinct spatiotemporal proteome expression at initiation of lung injury. *Am J Respir Cell Mol Biol* 2019;61:631–642.
11. Shepherd EG, De Luca D. New imaging tools allow bronchopulmonary dysplasia to enter the age of precision medicine. *Am J Respir Crit Care Med* 2020;202:924–926.
12. 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.
13. Thomson J, Rüegger CM, Perkins EJ, Pereira-Fantini PM, Farrell O, Owen LS, *et al.* Regional ventilation characteristics during non-invasive respiratory support in preterm infants. *Arch Dis Child Fetal Neonatal Ed* [online ahead of print] 27 Nov 2020; DOI: 10.1136/archdischild-2020-320449.
14. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proc Am Thorac Soc* 2009;6:272–277.
15. Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med* 2019;381:1248–1256.