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Baby's First Cries and Establishment of Gas Exchange in the Lung

In this issue of the *Journal*, the report from Tingay and colleagues (pp. 82–91) about the behavior of gases in the term infant lung presents new information about the initial aeration to air-breathing in a Cesarean section–delivered healthy term newborn who did not require any respiratory assistance (1). It builds on recent interest in how to aerate the newborn lung to minimize injury (2, 3). The initial aeration of the fluid-filled lung is perhaps the largest physiologic challenge for all mammals because other fetal organs that must work and are essential for fetal survival have been tested *in utero*. During the fetal period, poor cardiac function results in hydrops or intrauterine demise, impaired renal function leads to oligohydramnios and pulmonary hypoplasia, and disordered brain function can lead to contractures and arthrogryposis. The lung transition requires respiratory challenges and, as we are learning, elaborate coordination of pharyngeal reflexes to support airway patency and mechanisms to rapidly move the fetal lung fluid out of the airspace and into the interstitium of the lung and ultimately out of the lung (4). The fetal lung is not collapsed (Figure 1A): it has a normal FRC of about 30 ml/kg maintained by low protein content fluid (5).

The new information provided by Tingay and colleagues using breath-by-breath electrical impedance tomography shows that as the infants are transitioning to air-breathing, they have two distinct breathing patterns: crying and tidal breathing. Crying is the primary breathing that recruits FRC, which is achieved within 43 breaths (1). The initial gas flow goes primarily into the right lung to nondependent sections and is nonuniform (Figure 1B). Crying is associated with the expiratory braking of flow, which redistributes gas in the lung by pendelluft flow to preserve FRC (Figure 1C). These are unique patterns of breathing and gas flow that probably occur only during the neonatal transition to air-breathing. Inflation of the lungs also contributes to lung liquid clearance (6).

Do the results provide clinical insights to help guide strategies to assist the transition to air-breathing when assistance is needed? There recently has been great interest in how best to use continuous positive airway pressure to optimize aeration of the preterm usually surfactant-deficit infants to avoid pressure-related lung injury using sustained inflation (7). A recent randomized control trial of sustained inflation was stopped because of increased death in the intervention group. The cause of increased death in the sustained inflation group was not known (2). The results of Tingay and colleagues may provide a clue because of the preferred flow of gas to the nondependent lung regions, which could cause localized overinflation and injury. We have a bad habit of applying interventions to neonatal care before we understand the normal physiology. Tingay and colleagues have provided us with information about normal transition gas volumes to develop different, innovative strategies that might be more aligned with normal transitional physiology. There is other recent information about the complex gene expression changes in the lung around the transition to air-breathing (8). There was mRNA expression heterogeneity in lung cell type RNA, indicating cell stress and unfolded protein responses. The remarkable result using electrical impedance tomography is how rapidly the FRC is established. Some of the values are quite high, suggesting that there might be gas trapping.

Tingay and colleagues (1) have provided us with new information about $\dot{V}$ (ventilation with gas) but no information about $\dot{Q}$ (pulmonary blood flow). Hypoxic pulmonary vasoconstriction contributes to high fetal pulmonary vascular resistance, and ventilation with air or oxygen reduces pulmonary vascular resistance (9, 10). The infants in the study by Tingay and colleagues had gradually improving oxygenation from their initial median oxygen saturation as measured by pulse oximetry (Sp_{O_2}) of about 52% at 60 seconds to 78% by 360 seconds, so presumably, at least initially, there was diversion of pulmonary blood flow away from

Originally Published in Press as DOI: 10.1164/rccm.202102-0308ED on March 8, 2021

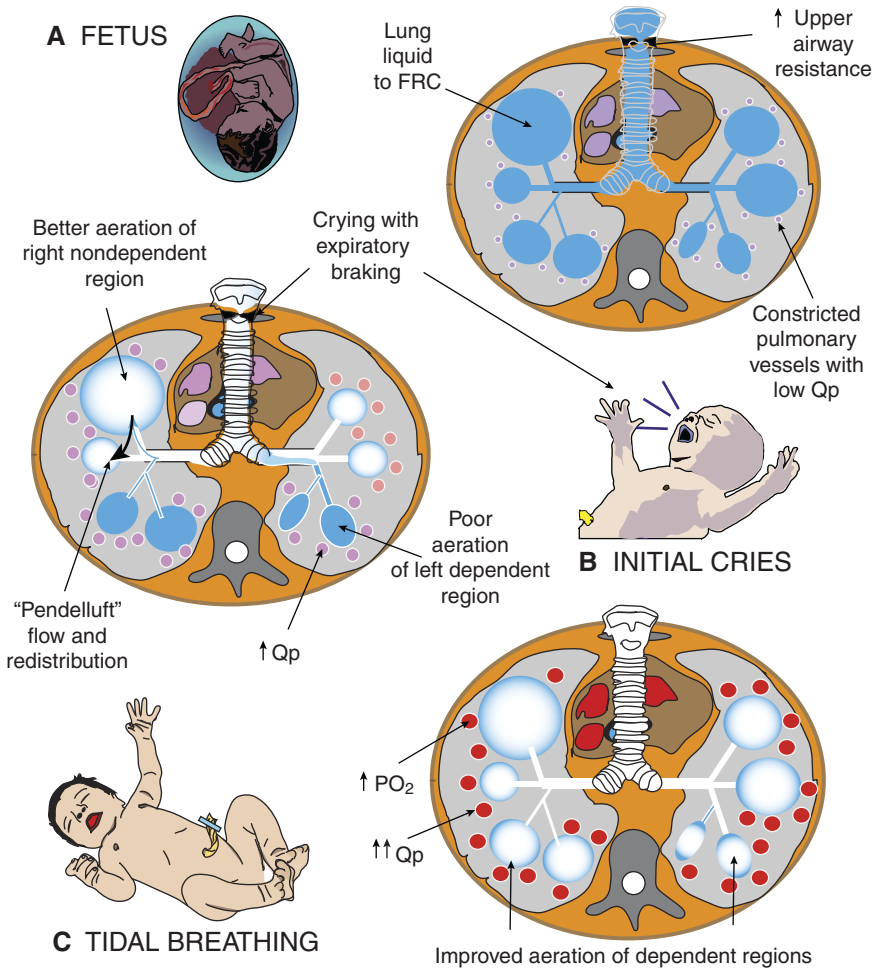

Figure 1. (*A*) During the fetal period, lung liquid fills the alveoli to FRC with slight positive pressure maintained by elevated upper airway resistance. Pulmonary blood flow is low, partly because of hypoxic pulmonary vasoconstriction. (*B*) The first few cries lead to asymmetric ventilation of right nondependent areas of the lung. Increased alveolar pressure plays a role in lung liquid clearance. Expiratory "braking" during crying and "pendelluft" flow leads to redistribution of ventilation to dependent regions of the lung. (*C*) Improved aeration of the dependent regions and pulmonary vasodilation associated with tidal respirations improves oxygenation. Qp = pulmonary blood flow. Illustration by Satyan Lakshminrusimha.

unventilated lung regions of the lung (initially the entire left lung) (11). More recent studies in rabbits have shown that unilateral ventilation of the right lung with air increases perfusion to both lungs (12). Increase in P_{O_2} and decrease in P_{CO_2} in the perfusing blood reduces vascular resistance in the nonventilated segment of the lung (13). These phenomena can transiently worsen $\dot{V}/\dot{Q}$ mismatch and contribute to low Sp_{O_2} (Figure 1B). However, the "pendelluft" flow, redistribution of gas with expiratory braking with crying (Figures 1B and 1C), and potential reversal of regional "pneumoconstriction" by improved flow (14) can lead to enhanced ventilation in these dependent segments, contributing to better matching of $\dot{V}/\dot{Q}$ and improved Sp_{O_2}. Further understanding of physiology of pulmonary blood flow may enable us to optimize inspired oxygen concentrations during resuscitation of extremely preterm infants (15).

There are probably new insights to be gained from this type of human physiological research to better guide clinical studies in neonatal resuscitation in other groups of high-risk patients, such as the very preterm infants with immature lungs and term infants with lung disease. ■

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

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