Loss of liquid from the lung lumen in labor:
more than a simple “squeeze”

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Physiologists have known for over a century that the lungs are filled with liquid during fetal life (53), but the origin of this liquid was uncertain until 1948 when Jost and Policard (35) challenged the then prevailing view that liquid in the lumen of the fetal lung came from intrauterine aspiration of amniotic contents (2). In studies designed to examine the ontogeny of the pituitary-adrenal axis, these French scientists ligated the tracheae of fetal rabbits and serendipitously discovered that over a period of 9 days, the lungs became distended with fluid (35). This observation, subsequently confirmed and expanded on by others (3, 32), established that the lung itself rather than the amniotic sac is the source of liquid that fills the lumen of the developing lung, thereby serving as a well-regulated template for fetal lung growth. Subsequent studies, most of them in sheep, showed that this liquid derives from chloride secretion across the respiratory epithelium (1, 51), a process that can be inhibited by diuretics that block Na-K-2Cl cotransport (18, 20, 56). In vitro studies using cultured tissue explants and monolayers of epithelial cells harvested from human fetal lung have provided convincing evidence that cation-dependent chloride transport, driven by epithelial cell Na-K-ATPase, is the mechanism by which liquid is secreted into the lumen of the mammalian lung during development (5, 40).

Rapid removal of liquid from potential airspaces is a key step in establishing the timely switch from placental to pulmonary gas exchange at birth. A sudden gush of fluid from the mouth often punctuates a baby’s birth, signaling the start of extrauterine life. This observation helped to promulgate what has come to be known as the “vaginal squeeze,” a notion that was introduced almost half a century ago by Karlberg et al. (36) to explain how liquid is removed from the lungs as air breathing begins. This concept was derived from intrathoracic pressure measurements that a group of Swedish investigators made during delivery of normal-term infants (36). They reported that “Once the head is delivered a pressure difference between the mouth and the thorax is created which would serve to express the amniotic fluid from the airways. This reasoning seems in agreement with the clinical observation that fluid flows out of the nose and mouth, sometimes as a jet, at this stage of delivery.” The report went on to say that “because the intrathoracic pressure variations during vaginal delivery appear to play a role in facilitating the subsequent aeration of the lung parenchyma, it may be speculated upon whether the absence of ‘the squeeze’ in infants delivered by Cesarean section may, at least in part, be responsible for the higher incidence of neonatal respiratory complications occurring in this group” (36). Although several reports have documented the importance of labor in facilitating lung liquid removal during birth (12–15, 23) and the adverse effects of a cesarean section without prior labor on the incidence and severity of neonatal respiratory distress (16, 17, 26, 49), it has taken the better part of four decades for scientists to clarify how liquid drains from the lungs around the time of birth. Although the vaginal squeeze is undeniably crucial in expelling the fetus from the introitus, mechanical compression of the thorax per se appears to have little, if any, impact on liquid drainage from the lungs during birth (12, 15). Indeed, the normal transition from liquid to air inflation of the lungs during parturition is considerably more complex than the characteristic oral gush at delivery would imply. As birth approaches near term gestation, the rate of liquid formation and the volume of liquid within the lumen of the fetal lung decrease (30, 39). These changes occur at a stage of lung development in which there is increased pulmonary expression of epithelial sodium channels and Na-K-ATPase (28, 34, 43, 48, 55) as well as increased activity of Na-K-ATPase in distal lung epithelial cells (11, 24, 34). Several investigators (8, 47, 54) have examined the bioelectric properties of monolayers of cultured lung epithelial cells obtained from near-term fetal rats, showing that these cells have the capacity to absorb sodium. Thus developmental changes in lung epithelial cell ion transport late in gestation, switching from predominantly chloride se-
cretion to predominantly sodium absorption near birth, appear to have an important role in preparing the lung for its pivotal postnatal adaptation.

What regulates the balance between secretion and absorption of lung liquid near birth? Several studies have demonstrated that hormonal changes occurring in the fetus just before and during labor, notably increased release of epinephrine from the adrenal medulla, may have an important role in triggering the switch from liquid secretion to absorption. In studies done with fetal lambs late in gestation, Walters and Olver (58) found that intravenous infusion of epinephrine or isoproterenol, but not of norepinephrine, led to the absorption of liquid from potential airspaces, an effect that β-adrenergic blockade with propranolol prevented. The same group of investigators subsequently showed that intraluminal administration of amiloride, a sodium transport inhibitor, blocked the effect of epinephrine on lung liquid absorption in fetal sheep (50). This finding suggests that β-adrenergic agonists stimulate sodium uptake by the lung epithelium, which, in turn, drives liquid from the lung lumen into the interstitium where it can be absorbed into the pulmonary circulation or drain through lung lymphatics into the systemic circulation (13). Tracheal instillation of dibutyryl cAMP (an analog of cAMP) also leads to the absorption of lung liquid in fetal lambs late in gestation (6, 59). The inhibitory effects of both dibutyryl cAMP and epinephrine on the net production of lung liquid increase with advancing gestational age, and both responses are attenuated by prior removal of the thyroid gland (6). Barker et al. (10) showed that replacement therapy with triiodothyronine after thyroidec- tomy restored the inhibitory effect of epinephrine on lung liquid production in fetal sheep. These investigators subsequently found that treatment of preterm fetal sheep with a combination of triiodothyronine and hydrocortisone may stimulate early maturation of epinephrine-induced absorption of lung liquid (7, 9). Another study (22) showed a synergistic effect of terbutaline, a β-adrenergic agonist, and aminophylline, a phosphodiesterase inhibitor, in switching lung liquid secretion to absorption in fetal lambs. In these studies, addition of amiloride to the lung liquid prevented its absorption. These observations support the view that as birth approaches, conditions that stimulate release of cAMP in the lung may trigger absorption of liquid from the lung lumen in response to transepithelial sodium efflux.

The decrease in lung liquid production that occurs in fetal sheep before birth may be related to a rise in plasma concentration of epinephrine late in labor (15). In fetal sheep, however, lung liquid production and lung water content often decrease before there is any detectable release of catecholamines (13, 23). Several reports have shown, however, that the concentration of β-adrenergic receptors in lung tissue increases late in gestation (25, 60, 61), which may make the lungs more responsive to the effects of epinephrine during labor (15).

During the past decade, the guinea pig has eclipsed the sheep as the experimental model of choice for studying developmental changes in lung fluid balance, confirming and, in some instances, expanding on observations that had been made previously on fetal and newborn sheep, goats, rabbits, and rats. Studies using excised lungs of fetal guinea pigs showed that Na-K-2Cl cotransport in the respiratory epithelium is the mechanism by which liquid secretion occurs in the fetal lung (56). Further studies using the same experimental model showed that the net production of lung liquid tends to decrease late in gestation (52) and that epinephrine, cAMP, cortisol, and aldosterone each can cause an abrupt decrease in fetal lung liquid formation (37, 38, 62). Studies using fetal and newborn guinea pigs have also shown that plasma epinephrine concentrations are elevated during labor and after birth (31, 42) and that inhibition of sodium transport across the respiratory epithelium slows the rate at which liquid is removed from the lungs postnatally (44, 45). The finding that propranolol inhibits lung liquid clearance in newborn guinea pigs (31) provides further evidence that epinephrine may play a critical role in perinatal clearance of lung liquid in this species. A recent study (4) indicated that the stimulatory effect of epinephrine on lung liquid clearance is coupled to increased postnatal pulmonary expression of amiloride-sensitive sodium channels, which is mediated, at least in part, by a perinatal increase in plasma cortisol concentrations (4). Thus the interaction of multiple hormones of adrenal origin appears to have a major regulatory role in converting the respiratory epithelium from a predominantly chloride-secreting membrane during fetal development to a predominantly sodium-absorbing membrane after birth.

This issue of the American Journal of Physiology-Lung Cellular and Molecular Physiology includes a paper describing experiments related to the mechanisms and regulation of lung liquid clearance in late-gestation guinea pigs after labor was induced by maternal injection of oxytocin (42). The results confirm the previous observations (15, 23, 45) made on near-term fetuses and newborn animals after the spontaneous onset of labor that events associated with parturition trigger absorption of liquid from the lung lumen across the respiratory epithelium into the pulmonary interstitium by a process that involves amiloride-sensitive sodium channels. This paper also shows that plasma epinephrine concentrations were significantly elevated in guinea pigs that had received oxytocin compared with those in control pups and that β-adrenergic blockade with propranolol markedly inhibited the rate of removal of lung liquid with and without prior treatment with oxytocin. These observations add to the growing body of evidence that the stress of labor, whether it occurs spontaneously or after oxytocin induction, stimulates release of epinephrine into the circulation, presumably increasing pulmonary cAMP and thereby increasing sodium absorption through amiloride-sensitive sodium channels on the luminal surface of the respiratory epithelium.

Early death from respiratory failure occurs in the absence of functional epithelial sodium channels (33),
whereas the essential role of epinephrine in this cascade of events is less clear-cut. At least two reports have indicated that absorption of lung liquid near birth does not depend on epinephrine. McDonald et al. (41) showed that irreversible blockade of β-adrenergic receptors in fetal rabbits did not prevent the normal reduction in lung water that occurs during parturition, and Chapman et al. (23) found that inhibition of β-adrenergic activity with propranolol did not prevent lung liquid absorption in fetal lambs late in labor. Both of these studies were done on living animals, whereas the studies reported by Norlin and Folkesson (42) in this issue of the Journal were conducted in lungs of fetuses after death. Thus, under in vivo physiological conditions, other hormones such as vasopressin (21, 57), cortisol, and aldosterone (7, 9, 37), all of which have been shown to reduce lung liquid production in fetal animals late in gestation, may substitute for epinephrine in stimulating sodium absorption in the respiratory epithelium. It is also possible that the mechanisms and regulation of lung liquid absorption may differ between species. For example, the bicarbonate concentration of lung luminal liquid is low (~2 meq/l) in fetal sheep and guinea pigs, whereas the bicarbonate concentration of lung liquid in fetal dogs and monkeys is similar to that of plasma (~25 meq/l) (27, 46). Thus one needs to be cautious in extrapolating results of studies done under specific experimental conditions in one species to the normal physiology of other species. Nevertheless, evidence is mounting to support the notion that the interaction of several hormones that are released late in gestation and during labor, including epinephrine, have an important role in regulating sodium-dependent lung liquid absorption near birth.

What is the clinical relevance of the aforementioned observations? First, there can be little doubt that delivery by cesarean section without prior labor greatly increases the risk of respiratory distress in human neonates. It remains to be determined whether induction of labor by oxytocin has the same effect on lung liquid clearance and associated respiratory function in newborn infants as it apparently has on near-term fetal guinea pigs. Although enormous progress has been made in recent years to help clarify how liquid is produced in the fetal lung and how it is removed during and after birth, there has been relatively little attention paid as to how this information relates to the human lung during development and how it might be applied therapeutically to alter lung growth before birth or to prevent respiratory distress after birth. Knowledge of how epithelial chloride secretion might be enhanced pharmacologically could prove useful in promoting expansion and growth of the fetal lung in situations that are known to be associated with pulmonary hypoplasia (congenital diaphragmatic hernia, prolonged oligohydramnios). β-Adrenergic agonists are often used to treat apparent bronchoconstriction in infants with chronic lung injury, and yet there has been little, if any, interest in determining the potential benefit of such therapy on lung liquid clearance in infants with acute respiratory distress. Recent reports (19, 29) indicate that intrapulmonary delivery of nitric oxide or surfactant may reduce the net production of liquid within the lungs of fetal sheep. It remains to be seen if these biologically active substances, which are so important in neonatal adaptation of the pulmonary circulation and terminal respiratory units, respectively, can be applied therapeutically to hasten liquid removal from the lungs in neonatal respiratory distress that is associated with alveolar edema. Lessons learned from the lung in labor need not be left to linger in the laboratory.

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