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Intrapulmonary Foam at Birth: An Adaptational Phenomenon

EMILE M. SCARPELLI[44]

Pulmonary Division, Department of Pediatrics, Albert Einstein College of Medicine, New York, New York, USA

Summary

The first inflation and deflation with air of excised lungs of mature fetal lambs and rabbits from the natural liquid-filled state invariably produced foam which was apparent in the trachea when transpulmonary pressure was <0 (lambs) and in terminal lung units (TLU) when monitored by stereomicroscopy (rabbits). Similarly, examination of neonatal lungs of lambs and rabbits that had breathed spontaneously (1 breath to 15 min) revealed bubbles in small airways and in TLU. Volume-pressure diagrams of excised lungs (lambs) revealed relatively low apparent opening pressures, low pressures at maximal volume, and appearance of foam in large airways after withdrawal of a volume of air equivalent to 30% or more of functional residual capacity (FRC) during deflation. The latter is consonant with the presence of bubbles in TLU. Studies of excised lungs indicated that additional foam may be produced during the second inflation. The extent to which subsequent breaths may contribute to foam production could not be determined, but it was apparent that the early neonatal lung (up to 15 min in our studies) is a three-phase system of intrapulmonary foam, free air, and liquid. The phospholipids of fetal pulmonary fluid (FPF) from which foam is produced were incorporated preferentially (in relation to the proteins) into the bubble films.

Speculation

Intrapulmonary foam at birth could play an important role in a number of vital adaptations that are known to occur. 1) Bubbles apposing the walls of TLU are air pockets within thin films across which gas exchange would be facilitated beginning with the first breath. 2) Intrapulmonary foam may play a role in maintenance of dilated airways during expiration and at end-expiration when transpulmonary pressures are high. 3) Oxygenation and distention of TLU by foam could be the earliest stimuli for rapid fall of pulmonary vascular resistance. 4) The phospholipids of bubble films could be immediate precursors of the alveolar lining layer that needs to be established quickly at birth. 5) The large thoracic gas volume to FRC ratio of neonatal lungs may be due, in part at least, to intrapulmonary foam. Whereas foam volume and foam production were not quantified in our studies, it appears that the duration of the "foam lung" state and the relative amounts of intrapulmonary foam and free air would depend on FPF volume at the time air breathing is begun and on the rate at which FPF is subsequently absorbed.

Immediate aeration of mammalian lungs at birth, which appears to have been demonstrated roentgenographically (11, 14, 18), would seem to be a most extraordinary accomplishment given the facts that 1) the fetal lung is filled with FPF at approximately FRC (33) and 2) absorption of FPF is only 50–70% complete after 2 hr of air breathing (17). The traditional concept of aeration of the lung at birth as a process in which the air and bulk liquid phases remain separate (1, 36) is difficult to sustain, since unabsorbed FPF should block alveolar-capillary gas exchange especially during the first breaths of extrauterine life. Also unexplained by the air-bulk liquid model is the observation that airways appear to be distended at the end of the first expiration (14) and the expectation that breathing movements of the neonate should produce a dispersion of air in liquid.

We have noted in newborn lambs and kids that FPF leaves the trachea during the first inhalation of air, that foam appears in this airway during subsequent breaths, and that tracheal foam disappears rapidly as the air lung is established (30, 32). We have now studied the phenomenon directly in excised lungs and lungs *in situ* of both lambs and rabbits. We find that intrapulmonary foam is produced invariably when the lung is first inflated with air; that the very early neonatal lung is a three-phase system of free air, foam, and liquid; and that formation of intrapulmonary foam may be a transient adaptational phenomenon of importance to the cardiopulmonary adjustments that take place at birth.

METHODS

We studied fetal and neonatal lungs of mature (>0.9 gestation) lambs and New Zealand White rabbits. Fetal lungs were excised, whereas neonatal lungs were observed *in situ.*

FETAL LAMB LUNGS

With induction and maintenance of light anesthesia in the ewe, six mature lamb fetuses were prepared *in utero* by insertion of an ascending aortic catheter and a tracheal cannula for sampling FPF using methods described previously (33). FPF volume was determined by the radioiodinated serum albumin (RISA)-dilution method in five fetuses and estimated as 30 ml/kg body wt in one fetus (33). Fetuses were delivered through a hysterotomy and the cord was ligated as an overdose of sodium pentobarbital, 30 mg/kg iv, was given. Trachea, lungs, and heart were removed rapidly en bloc without loss of FPF and the heart was cut away at the atria and major arteries. A summary of fetal condition and experimental procedures is given in Table 1. Only fetuses 2 and 3 were from the same ewe.

Quasistatic air volume-pressure (VP) diagrams were registered from the FPF-filled state for the lungs of fetuses 1–5, using fixed volume changes of 10 ml at 20-sec intervals. Air inflation was stopped after a volume equivalent to FRC, either as estimated or as determined by RISA-dilution, was delivered (V_{max}) (39). Air was then removed from the lung (10-ml decrements, 20-sec intervals) until foam appeared in the tracheal cannula and the trachea collapsed as intratracheal pressure fell below atmospheric pressure, invariably at a volume greater than the preinflation volume. For fetuses 4 and 5 this was followed by a second inflation to an arbitrarily selected V_{max} 20% greater than the first V_{max} in order to mimic volume changes that may occur at birth (18). During the second deflation foam appeared and the trachea collapsed at higher volumes than during the first deflation. This general protocol was modified for fetus 6 as follows: The FPF-filled lungs were inflated rapidly with air, 1.5-sec inflation time, then deflated rapidly until foam and tracheal collapse appeared.

Samples of FPF and foam were obtained for analysis. Foam was drained for 30 min, lyophilized, and dispersed in normal

Table 1. *Summary of fetal condition and experimental procedures on excised lamb fetal lungs*[1]

Fetus	Pregnancy	Body wt (kg)	(*In utero*) PaO_2	$PaCO_2$	pH	FPF vol[2] ml	ml/kg	V-P diagrams 1st air	2nd air	Pooled foam V/V	recovered
1	Single	5.57	21	40	7.25	189	33.9	(+)	(−)	5:1	>20
2	Triplet	2.73	24	37	7.32	82 (estim.)	30 (estim.)	(+)	(−)	5:1	>10
3	Triplet	2.73	22	36	7.30	102	37.3	(+)	(−)	(−)	(−)
4	Twin	3.56	29	41	7.36	117	32.9	(+)	(+)	(−)	(−)
5	Twin	3.10	22	34	7.34	102	33.0	(+)	(+)	(−)	(−)
6	Twin	3.37	20	34	7.35	110	32.6	[3]	(−)	(−)	(−)

V/V: ratio of volume of foam to volume of liquid from foam.

[1] (+) indicates study was done; (−) indicates study was not done.

[2] Determined by RISA-dilution for all subjects except fetus 2 for which it was estimated according to Ref. 33.

[3] Lungs inflated rapidly, 1.5 sec, to V_{max}.

NaCl solution. FPF and foam dispersions were extracted with $CHCl_3$-CH_3OH, 2:1. The chloroform phase was analyzed for total lipid phosphorus and for lipid composition by thin layer chromatography by methods described previously (27). Total protein concentration of the aqueous phase was determined by the method of Lowry *et al.* (21) and protein composition by 7.0% polyacrylamide gel electrophoresis (22).

NEONATAL LAMB LUNGS

Under light maternal anesthesia (33) five mature lambs were delivered through a hysterotomy, permitted to breath spontaneously for 2–15 min (normal respiratory rate, heart rate, blood pressure, and activity), then killed by an overdose of sodium pentobarbital. The trachea was opened immediately by cutting longitudinally with scissors and the incision was extended to the smallest airways possible.

FETAL RABBIT LUNGS

Eleven mature rabbit fetuses from eight dams were delivered through a hysterotomy and injected with an overdose of sodium pentobarbital ip. Air inflation was prevented as the trachea was cannulated, and the trachea, heart, and lungs were removed en bloc. The heart was cut away and the lungs placed under a stereo microscope (Wild Heerbrugg, model M5, Wild Corp., Switzerland). Lungs were either inflated with syringe to Vmax (30 μl air/g body wt) and deflated (five preparations) or inflated and deflated with fractional increments (six preparations) under microscopic observation to determine sequence and course of gas movement in the lungs. Total time from delivery to first inflation was <10 min.

NEONATAL RABBIT LUNGS

Forty-five mature rabbit fetuses from 18 dams were delivered through hysterotomy, permitted to breath spontaneously, then killed by overdosage with sodium pentobarbital. The trachea was cannulated and the anterior right thoracic cage was excised to permit direct microscopic observation of the lung *in situ.* Thus we were able to view lungs immediately after normal spontaneous breathing for <1 min (10 preparations) and for 1 to 15 min (35 preparations).

To substantiate further the viability of rabbit subjects, at least one littermate, randomly selected from each pregnancy, was delivered through hysterotomy and observed for 6–24 hr. Each was normal as judged by color, activity, "cry," sucking, and respirations.

RESULTS

Intrapulmonary foam was seen by gross and/or by microscopic inspection of each preparation.

FETAL LAMB LUNGS

A composite of the first VP diagrams of fetuses 1–5 is given in Figure 1. Of interest are the observations that apparent opening pressure (40) was low; foam appeared in the tracheal cannula during deflation; the trachea collapsed when intrapulmonary pressure was below atmospheric pressure; and 50–70% of the air introduced during inflation remained in the lungs at "resting volume" (RV). The second VP diagram (fetuses 4 and 5) is remarkable in that apparent opening pressure was less; the pressure at V_{max} was less; and RV was greater than the first (Fig. 2). The lungs that were inflated rapidly (fetus 6, 1.5-sec inflation time) also contained foam in the airways upon deflation and retained 50% of the air volume at RV.

Some physicochemical properties of FPF and foam are given in Table 2 and distribution of lipid and protein is shown in Figure 3. The [phospholipid]/[protein] was about 17 times greater in foam than in FPF, suggesting phospholipids had been taken up selectively in foam films as they were formed in the lungs. Since we did not quantify neutral lipids, we cannot comment on their possible selective recovery in foam. However, the distribution of neutral lipids and phospholipids is the same in FPF and foam (Fig. 3). Phospholipids include phosphatidylcholine in highest concentration, sphingomyelin, and spots that may correspond with phosphatidylethanolamine and phosphatidylglycerol. In contrast with lipids, the distribution of proteins was not the same (Fig. 3): Although FPF included albumin > prealbumin > "transferrin" > postalbumin > slow moving band, the proteins of foam included slow moving band and trace amounts of albumin.

NEONATAL LAMB LUNGS

Foam was present in distal airways of each lamb that had breathed normally for 2–15 min. Additional foam appeared when the lungs were squeezed manually.

FETAL RABBIT LUNGS

As expected, the first air inflation of mature fetal lungs to Vmax produced quick expansion of TLU (41). Thus it was difficult to visualize sequential topographic changes as they occurred before expansion of the units. When the lungs were deflated, most of the units remained aerated as <50% inflation volume could be withdrawn and bubbles appeared in major bronchi and trachea.

When small volume transfers of air were used for inflation and deflation under microscopic control, movement of air through the airways and into the periphery of TLU was visible. Under these conditions it was clear that bulk air displaces bulk FPF in larger airways as air first enters the lung. As air entered the smallest airways, what appeared to be early bubble formation was seen (Fig. 4). When air was withdrawn before the apparent bubble formed, the airway refilled with liquid. If, on the other hand, inflation was continued, the TLU expanded rapidly to the periphery. With deflation from this point, the periphery of the TLU

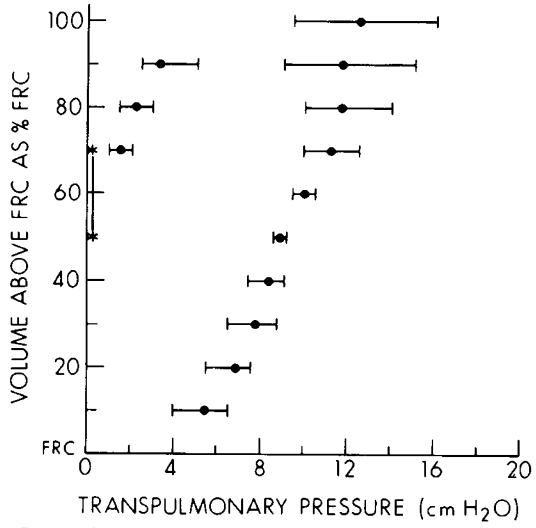

Fig. 1. Composite volume-pressure diagram of first inflation with air of excised mature lamb lungs, fetuses 1–5. Lungs contained FPF at volume equivalent to FRC before air inflation. Total volume of air added was equal to volume of FPF, *i.e.*, equal to FRC. ●: mean; ⊢ ⊣: range; |: volume at which foam appears in trachea and trachea collapses when $P < 0$.

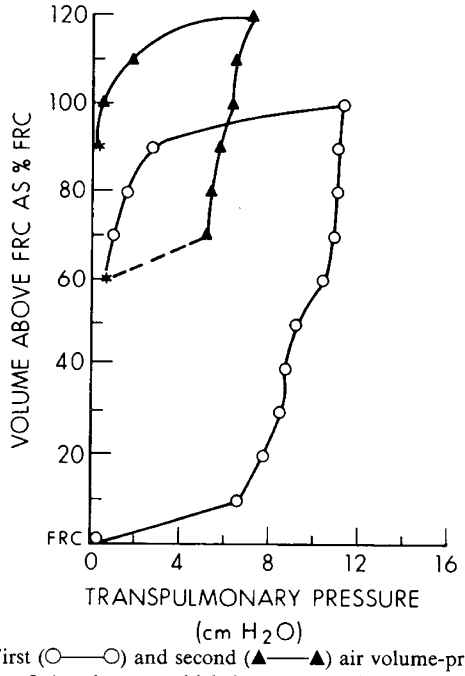

Fig. 2. First (○——○) and second (▲——▲) air volume-pressure diagrams of fetus 5. *: volume at which foam appears in trachea and trachea collapses when $P < 0$.

Table 2. *Some physicochemical characteristics of FPF and foam from FPF*[1]

Foam to liquid ratio (V/V)[2]	5:1
FPF protein (μg/ml)	526
FPF phospholipid (μg/ml)	50
FPF [phospholipid]/[protein]	0.095
Foam [phospholipid]/[protein]	1.667

[1] Averages of data from fetuses 1 and 2 in which individual determinations did not vary by more than 5%.

[2] Determined by measuring the volume of liquid obtained from a volume of foam at atmospheric pressure after the foam was collapsed by addition of octyl alcohol.

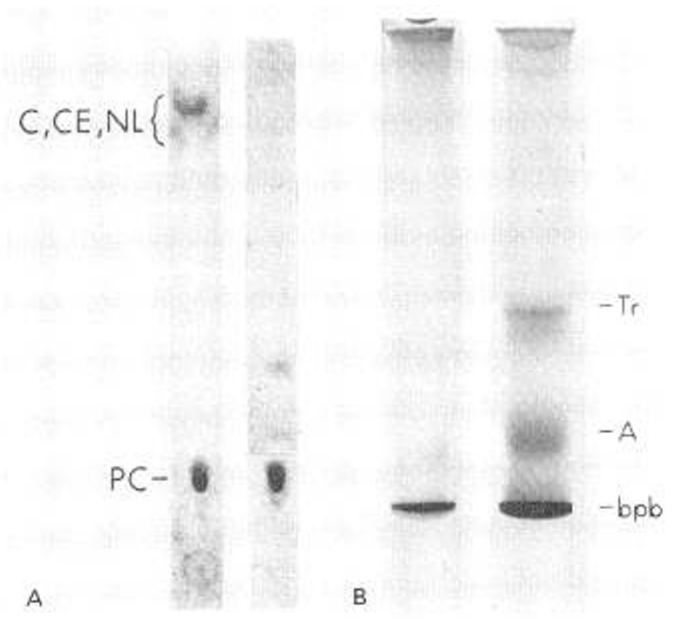

Fig. 3. *A:* thin layer chromatograms of lipid extracts from foam. *Left:* I_2 stain shows spots at front that migrate as cholesterol-cholesteryl esters (C/CE) and neutral lipids (NL) and darkest spot closest to origin, phosphatidylcholine (PC). [Phospholipids that migrated ahead of PC stained lightly with I_2]. *Right:* molybdenum stain for phospholipids shows phosphatidylcholine below the drawn line; sphingomyelin (the faint spot below phosphatidylcholine); and two faint spots above the drawn line which are phospholipids that may correspond to phosphatidylethanolamine and phosphatidylglycerol, the faster and slower spots, respectively. *B:* polyacrylamide disc gel electrophoresis. *Right:* fetal pulmonary fluid. Darkest band is bromphenol blue (bpb) indicator followed by a prealbumin, albumin (A), a band between A and the band with an R_f like that of transferrin (Tr), and a slow moving band near the origin. *Left:* foam. Darkest protein band is the slow moving band near the origin. There is also a faint band in the albumin region.

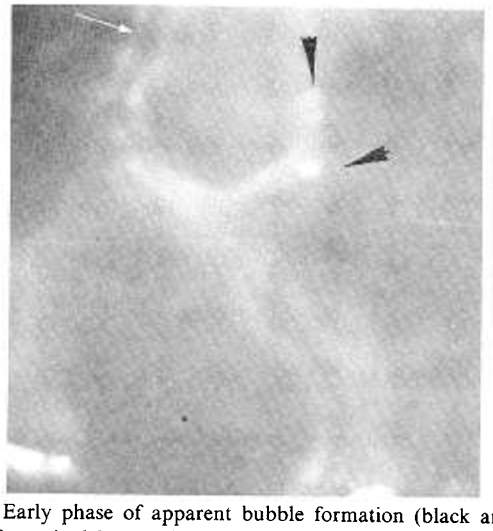

Fig. 4. Early phase of apparent bubble formation (black arrows) in airways of terminal lung unit of rabbit. When air is withdrawn at this point, liquid refills airways. Homogeneous background is normal appearance of fetal liquid-filled lung. White arrow points to pulmonary blood vessel. Magnification ×45.

remained inflated, whereas some airways retained air and others refilled with liquid. During reinflation from this point, bubbles as well as free air moved freely toward the periphery of TLU and expanded previously unexpanded portions of the units (Fig. 5). It

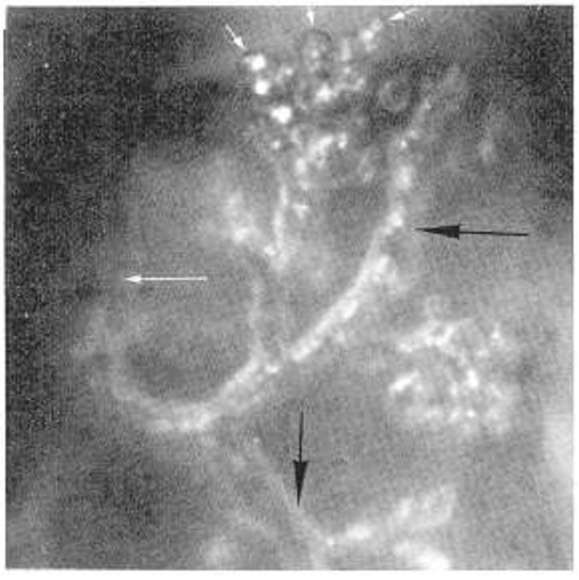

Fig. 5. Inflation after "deflation" (see text). Bubbles, which ultimately move into the previously liquid-filled periphery and expand it, are seen in airways (horizontal black arrow). Other airways contain free air (*e.g.*, vertical black arrow). Bubbles in periphery of TLU (short white arrows) give appearance which is indistinguishable from that of periphery with free air. Pulmonary blood vessel is seen (horizontal white arrow). Magnification ×45.

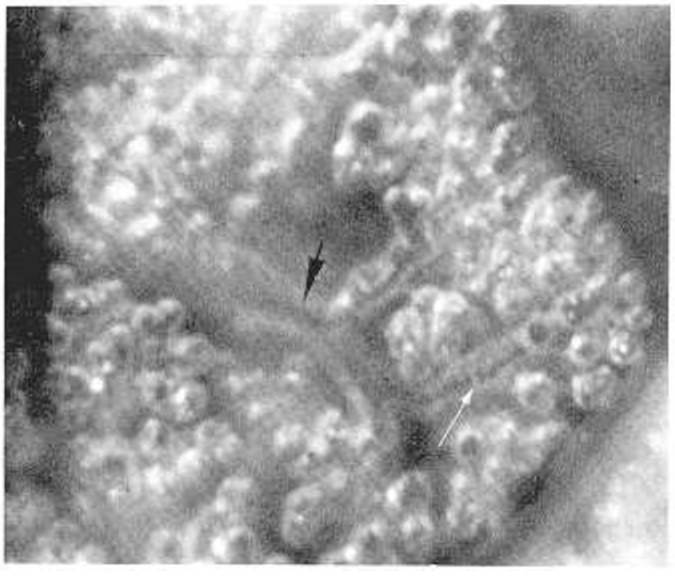

Fig. 6. Progressive inflation of lungs shows bubbles (white arrow) and free air (black arrow) in airways. Magnification ×45.

is also of interest that bubbles within airways could be moved easily by the experimenter with a probe in contact with the outer wall of the airway.

Another phenomenon was seen in a very small number of TLU. Although there was no indication of bubble formation during inflation, once inflated the TLU was indistinguishable from other units into which bubbles had been transferred. However, in contrast to the latter, these units refilled with liquid during deflation, the bulk liquid moving from periphery to center of the unit and then into larger airways. In other studies not reported here (34), we found this phenomenon of refilling units to be characteristic of the lungs of immature rabbit fetuses.

As mature lungs were inflated to progressively larger volumes, the refilling phenomenon became less frequent as more TLU remained expanded upon deflation to zero transpulmonary pressure. At this point both bubbles and free air were seen in airways (Fig. 6) and bubbles appeared rapidly at the lung surface when it was incised superficially.

NEONATAL RABBIT LUNGS

Of the 10 lungs studied *in situ* after <1 min spontaneous breathing, three (including one from a subject that had taken one breath) appeared uniformly well aerated after the right anterior thoracic cage was removed. The other lungs were aerated diffusely but not maximally; *i.e.*, there was brown-red mottling indicative of FPF-filled regions. At RV, bubbles were seen in all size airways and appeared at the lung surface when it was incised. The TLU of well aerated lungs were uniformly expanded, whereas "diffusely aerated" lungs contained expanded TLU apparently randomly interspersed with liquid-filled units. Photomicrographs that take advantage of shadow casting show expanded and liquid-filled areas (Fig. 7).

Of 35 lungs studied after 1–15 min of spontaneous breathing, foam was *not* visible in the tracheas of 10. In the remaining 25 lungs, tracheal foam density ranged from trace amounts adhering to the tracheal surface to bulk quantities that appeared after the chest was opened (lung at RV) and occupied up to half the tracheal cross section. Bubbles could be identified and manipulated in a number of TLU of each lung (Figure 8).

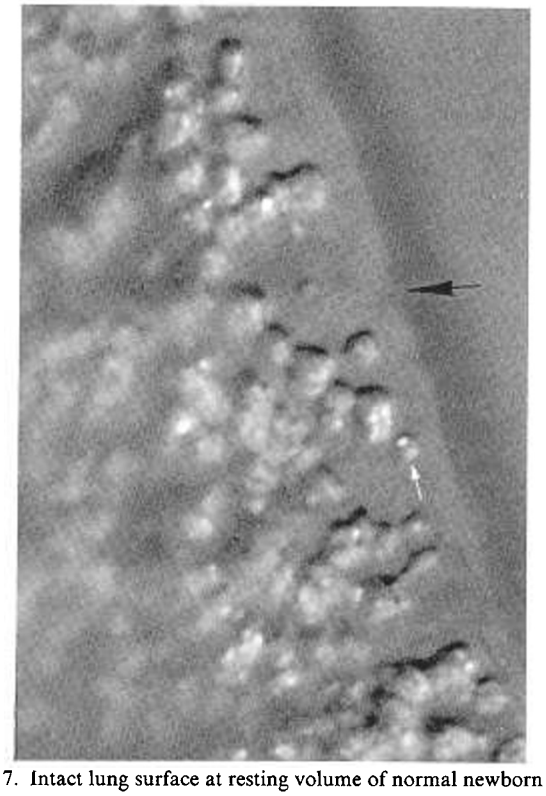

Fig. 7. Intact lung surface at resting volume of normal newborn rabbit which had breathed spontaneously for 45 sec. Black arrow points to lung edge. Flat, homogeneous surface is of areas that are still liquid filled. Raised or distended surface is of areas that contain air; bubble forms (*e.g.*, white arrow) are apparent.

DISCUSSION

The present studies indicate that intrapulmonary foam is produced during the first breath(s) at birth as air enters the previously liquid-filled mature fetal lung. They confirm and extend our previous observations (30, 32) and provide insight into the possible physiologic significance of this apparently normal adaptational phenomenon.

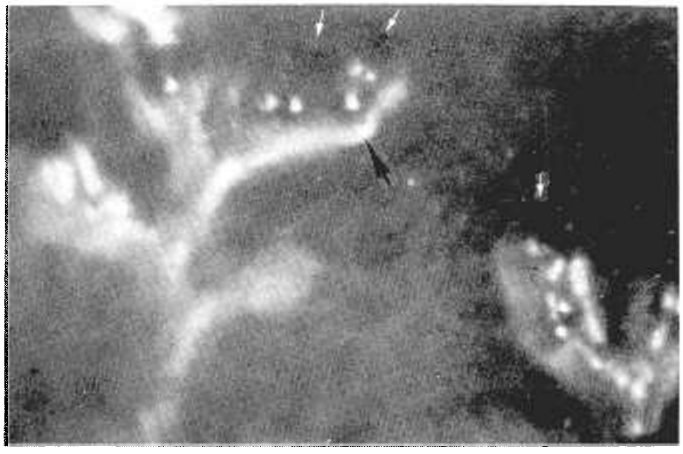

Fig. 8. Aerated periphery of TLU of normal newborn rabbit which had breathed spontaneously for 1.5 min. White arrows point to limiting margin of periphery of TLU which, in right lower unit, is so thin as to be indistinguishable from the background. Bubbles within periphery could be manipulated by experimenter. Other aspects of the peripheral margin (black arrow, white border) appear relatively thick and probably represent displaced liquid. Magnification ×94.

FOAM PRODUCTION AND VP DIAGRAM

Although intrapulmonary foam production during the first inflation(s) of both living and excised fetal lungs has not been reported heretofore, certain theoretic considerations indicate that foam production is indeed expected as air enters the liquid lung for the first time (see *Appendix*). The present studies confirm this expectation by direct observation of both excised lungs and lungs *in vivo*.

Others have shown that the observed progressive air trapping with continued ventilation of degassed excised lungs of adult rats is consistent with bubble formation during inflation (12). They indicate that bubbles are the main cause of trapped air and support previous observations of bubbles and air trapping in analogous experiments on adult lungs (9, 10, 25, 26). Because the fetal lung is liquid filled, it is not surprising that apparent foam production is several times greater in the fetus after the first air inflation than it is in the degassed adult lung (compare Fig. 2 this paper with Fig. 2 of Ref. 12). A practical consequence of these observations is that intrapulmonary foam must now be taken into account in analyses of VP diagrams of perinatal lungs for determination of lung stability and lung maturity (3, 7, 19, 36, 37). Our studies show that foam is one determinant of the position of the deflation curve and of the magnitude of RV, the accepted indices of stability. Increasing amounts of foam move the curve to the left and increase RV (Figs. 1 and 2), *i.e.*, indicate greater stability.

The present studies agree in several ways with those of Karlberg *et al.* (18), who recorded VP diagrams of newborn infants at the onset of breathing: 1) Once opening pressure is achieved *in vivo*, the human neonatal lung inflates rapidly to a maximal volume and retains a substantial fraction of this volume at end-expiration when positive intrapleural pressures are produced. 2) The second breath requires smaller apparent opening pressures, achieves higher maximal volumes with lower distending pressures, and results in larger retained volumes at end-expiration. We differ from this group in that apparent opening pressures in the excised lungs are lower than those recorded from newborn infants. We cannot explain the difference but suggest the possibilities that transpulmonary pressure was actually less than intraesophageal pressure in the infants or that the excised lungs contained more FPF, hence wider airways, than infants delivered by the vaginal route. With regard to opening pressures in the lamb, our VP diagrams are in closer agreement with those reported by Strang (36) who, however, did not report FPF volume before the first inflation.

FOAM PRODUCTION AT BIRTH

Implicit in the concept of intrapulmonary foam are the assumptions that 1) bubbles offer little resistance to breathing after the first breath and 2) bubble films collapse rapidly as FPF is absorbed. With regard to the first point, this study shows that intrapulmonary foam does not increase static resistance of the lung to inflation. Indeed the converse is true (Figs. 1 and 2). Although resistance to air flow was not measured, it is noted that dynamic resistance would be influenced by the force required to shear lamellae of foam films from airway surfaces. This force is proportional to the number of lamellae (n), surface tension (γ), radius (r), and average angle (θ) between lamellae and wall, *i.e.*, $F = 4\pi n\gamma r \cdot \cos\theta$. If γ of the pulmonary bubble films, in which phosphatidylcholine is the principal phospholipid, is similar to that of the alveolar lining layer [*i.e.*, if γ is zero or near zero (24, 29)], F is negligible. Our observations of bubble mobility during inflation and deflation, and the ease with which bubbles could be manipulated, are in accord with this concept. The second point, film collapse, is discussed below.

In contrast with the traditional concept that initial aeration of the lungs at birth is a process in which bulk air moves bulk liquid peripherally into TLU (1, 36), the present model of intrapulmonary foam is in accord with the cardiopulmonary adaptations that are known to occur.

1. Bubbles apposing the walls of TLU (Figs. 5 and 8) are air pockets ($PO_2 \cong 149$ mm Hg; $PCO_2 \cong 0$) within thin films across which gas exchange with capillaries and perhaps precapillary vessels (35) would be facilitated. This is in accord with the rapid rise of pulmonary venous PO_2 and fall of PCO_2 during the first minutes of air breathing at birth (23). Conversely, immediate and sustained gas exchange with apparent spread and retention of FPF in the peripheral parts of the lung (14) are not supported by the traditional air-bulk liquid model (1, 36): a) Since little absorption of FPF is expected during the first breath(s) (13, 17), the liquid in TLU would be a barrier to gas exchange. b) Inasmuch as adsorption times of surfactants from unagitated bulk liquid to the air-liquid interface are probably orders of magnitude greater (28) than the 1–2 sec of the first respiratory cycle (14), surface tension in the air-bulk liquid model would be high and FPF would tend to refill the TLU on expiration. In addition, high positive intrapleural pressures (18) would enhance refilling.

2. Rapid oxygenation of capillaries and precapillary vessels and mechanical distention of TLU (Fig. 7) could be the earliest stimuli for rapid fall of pulmonary vascular resistance and increase of pulmonary blood flow at birth. This is in accord with the generally accepted ideas that the major factor sustaining high fetal pulmonary vascular resistance is relative hypoxia and that mechanical distention of the lung at birth augments the lowering of pulmonary resistance (4).

3. Rapid and apparently preferential incorporation of phospholipids into bubble films could establish these films as precursors of the alveolar lining layer, which must be formed rapidly to insure stability of the neonatal air lung (31). The production of surfactant-rich foam *in situ*, as demonstrated in the present studies, is analogous to the classical laboratory procedure for concentrating surfactants by "foam fractionation" in glass columns (28), a procedure used by Enhorning *et al.* (8) to concentrate the phospholipids of lamb FPF *in vitro*. Absorption of bulk FPF from TLU (13), which presumably begins as the lungs are aerated and pulmonary blood flow increases (17, 31), should promote hypophase drainage of bubble films and collapse of the bubbles. Continuous transfer of oxygen, which is related to FPF absorption insofar as both are enhanced by increased capillary flow, would also accelerate the rate of collapse.

4. Inasmuch as both intrapulmonary free air and foam would be included in measurement of thoracic gas volume (TGV), whereas foam would not be included in measurements of FRC, TGV/FRC should be >1.0 at the onset of breathing. This has been shown to be true for newborn infants studied as early as 4–5 hr of life (20, 38). The "trapped gas" could be due, at least in part,

to intrapulmonary foam and the rate at which TGV/FRC progresses to unity (20, 38) could be an expression of the rate at which all vestiges of foam disappear.

5. Bubble turnover in the lung should be determined by a number of physicochemical properties (Ref. 2, p. 159) which have not been defined or quantified for the early neonatal lung. Nonetheless, it is apparent (see *Appendix*) that both bubble production and disruption would be influenced essentially by the availability of bulk liquid (FPF) and its constituent surfactants. If, in addition, bubble collapse is influenced by the rate of FPF absorption and O_2 transfer as suggested above, we may conclude that the duration of the foam lung state and the relative amounts of intrapulmonary foam and free air depend on FPF volume at the time air breathing is begun and on the rate at which FPF is subsequently absorbed.

CONCLUSIONS

Intrapulmonary foam is produced during the first breath(s) of extrauterine life as air enters the previously liquid-filled lung of the mature fetus. Bubbles appear to be produced in the smallest airways and are present in airways and periphery of terminal lung units. Although the volume and subsequent rate of foam production were not quantified, it is apparent that the neonatal lung is a three-phase system of intrapulmonary foam, free air, and liquid during the first 15 min (the limits of our experiments) of spontaneous air breathing. The conventional model of the air-bulk liquid neonatal lung is not supported by these studies which, along with the finding that bubble films apparently preferentially incorporate phospholipids, indicate that intrapulmonary foam production is an adaptational phenomenon of importance to the cardiopulmonary adjustments that are made at birth.

APPENDIX

Certain broad estimations can be made regarding expected production of foam by dispersion of inspired air in FPF during the first breath. First, however, it should be noted that a foam to liquid ratio of 5:1 (which, because of the relatively short drainage period used, probably includes bulk liquid that was not part of the foam films) (Table 2) indicates that even after the "vaginal squeeze," sufficient FPF would remain in the lungs to yield, theoretically, quantitative production of foam. Thus, for example, even if 20 ml FPF were expressed from the lungs by vaginal compression (18), a 3.4-kg infant with an initial FPF volume of 102 ml (33) would have sufficient FPF remaining to produce foam quantitatively from a first breath of 62 ml air (18). However, quantitative production of foam, as well as uniformity of bubble size and frequency, are probably not achieved (as indicated in the present study) because the airways, collectively, do not function as a perfect disperser or sparger, *i.e.*, gas distribution may not be uniform and airway length and orifice size vary.

Although we know of no direct precedent upon which calculation of the liquid lung's ability to produce foam *in situ* and *in vivo* may be based, we may speculate to some degree. Thus, to continue the example of the 3.4 kg infant, we will assume 1) that bubbles are formed in distal airways as suggested by the present studies; 2) that for the infant these are the distal respiratory bronchioles (an assumption which permits estimation of number of airways from published data, with the understanding that we do not exclude the possibility of bubble production in other airways); 3) that the number of distal respiratory bronchioles is 22.4×10^3, *i.e.*, one-tenth the adult number (6, 16); 4) that bubble production takes place primarily during inspiration as suggested by the studies of Frazer and Weber (12); and 5) that total volume flow through the bronchioles is 62 ml/sec (1-sec inspiration; neglecting anatomic dead space). Consequently, mean flow rate through each distal bronchiole would be 27.7×10^{-4} ml/sec. If internal diameter of distal bronchioles were 220 μm and if FPF were water [both invalid assumptions which, however, permit comparison with published data for nonbiologic systems (Ref. 2, p. 41)] bubble frequency from each bronchiolar orifice should be about 1^{-2}/sec.

However, the following considerations indicate that bubble frequency can in fact be much higher. 1) Human neonatal bronchiolar internal diameter is probably closer to 100 μm (5) so that linear velocity and bubble frequency would be considerably higher than predicted from the data of Bikerman (Ref. 2, p. 41). Interestingly, internal diameter of the airways of terminal lung units of neonatal rabbits during inflation (Figs. 6, 8, and 9) ranged from 40–90 μm. 2) The surface active phospholipids of FPF (Table 2, Fig. 4) should increase bubble frequency by enhancing bubble detachment (Ref. 2, pp. 34, 44) as the bubble is attracted to the peripheral epithelial walls (Figs. 8 and 12). 3) In addition, the smaller orifice size in the lung and the low surface tension of pulmonary phospholipids would result in bubbles several orders of magnitude smaller than predicted from the data from Bikerman (2) that were used in the preceding paragraph.

These considerations indicate that intrapulmonary foam production at the onset of breathing is indeed a phenomenon to be expected and the expectation is verified by the present studies. Important questions regarding quantification of foam, its volume relative to the volume of intrapulmonary free air, its persistence in the early neonatal period, and its relationship to fetal maturation and neonatal lung stability await further investigation.

REFERENCES AND NOTES

1. Avery, M. E., and Fletcher, D. B.: The Lung and Its Disorders in the Newborn Infant, 3rd ed., p. 29 (W. B. Saunders Co., Philadelphia, 1974).
2. Bikerman, J. J.: Foams (Springer-Verlag, Göttingen, 1973).
3. Corbet, A. J. S., Flax, P., and Rudolph, A. J.: Reduced surface tension in lungs of fetal rabbits injected with pilocarpine. J. Appl. Physiol., *41:* 7 (1976).
4. Dawes, G. S.: Foetal and Neonatal Physiology, p. 79 (Year Book Medical Publishers, Chicago, 1968).
5. Doershuk, C. F., Fisher, B. J., and Matthews, L. W.: Pulmonary physiology of the young child. In: E. M. Scarpelli and P. A. M. Auld: Pulmonary Physiology of the Fetus, Newborn and Child (Lea & Febiger Publishers, Philadelphia, 1975).
6. Dunnill, M. S.: Postnatal growth of the lung. Thorax, *17:* 329 (1962).
7. Enhorning, G.: Photography of peripheral pulmonary airway expansion as affected by surfactant. J. Appl. Physiol., *42:* 976 (1977).
8. Enhorning, G., Fujiwara, T., and Adams, F. H.: Surface active material in fetal lung fluid concentrated by foaming. Tohoku J. Exp. Med., *84:* 250 (1964).
9. Faridy, E. E.: Effect of hydration and dehydration on elastic behavior of excised dog's lungs. J. Appl. Physiol., *34:* 597 (1973).
10. Faridy, E. E., and Permutt, S.: Surface forces and airway obstruction. J. Appl. Physiol., *30:* 319 (1971).
11. Fawcitt, J., Lind, J., and Wegelius, C.: The first breath. Acta Paediat. Suppl., *123:* 5 (1960).
12. Frazer, D. G., and Weber, K. C.: Trapped air in ventilated excised rat lungs. J. Appl. Physiol., *40:* 915 (1976).
13. Gonzalez-Crussi, F., and Boston, R. W.: The absorptive function of the neonatal lung. Lab. Invest., *26:* 114 (1972).
14. Hirvonen, L., Peltonen, R., and Peltonen, T.: Disappearance of tracheobronchial fluid at birth in the lamb. Ann. Chir. Gynaecol. Fenn., *64:* 170 (1975).
15. Hislop, A., and Reid, L.: Development of the acinus in the human lung. Thorax, *29:* 90 (1974).
16. Horsfield, K., and Cumming, G.: Morphology of the bronchial tree in man. J. Appl. Physiol., *24:* 373 (1968).
17. Humphreys, P. W., Normand, I. C. S., Reynolds, E. O. R., and Strang, L. B.: Pulmonary lymph flow and the uptake of liquid from the lungs of the lamb at the start of breathing. J. Physiol., *193:* 1 (1967).
18. Karlberg, P., Cherry, R. B., Escardo, F. E., and Koch, G.: Respiratory studies in newborn infants. II. Pulmonary ventilation and mechanics of breathing in the first minutes of life, including the onset of respiration. Acta. Paediat., *51:* 121 (1962).
19. Kotas, R. V., and Avery, M. E.: Accelerated appearance of pulmonary surfactant in the fetal rabbit. J. Appl. Physiol., *30:* 358 (1971).
20. Krauss, A. N., and Auld, P. A. M.: Pulmonary gas trapping in premature infants. Pediat. Res., *5:* 10 (1971).
21. Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J.: Protein measurement with the Folin phenol reagent. J. Biol. Chem., *193:* 265 (1951).
22. Narayan, K. A.: The influence of polyacrylamide concentration on human and rat serum lipoprotein patterns. Anal. Biochem., *18:* 582 (1967).
23. Oliver, T. K., Jr., Demis, J. A., and Bates, G. D.: Serial blood-gas tensions and acid-base balance during the first hour of life in human infants. Acta Paediat., *50:* 346 (1961).
24. Pattle, R. E.: Properties, function, and origin of the alveolar lining layer. Nature, *175:* 1125 (1955).
25. Pattle, R. E.: Properties, function, and origin of the alveolar lining layer. Proc. Roy. Soc. London, *240:* 148 (1958).
26. Radford, E. P., Jr.: Static mechanical properties of mammalian lungs. In: W. O. Fenn and H. Rahn: Handbook of Physiology: Respiration, Vol. 1, Sect. 3, Chap. 15 (The Williams & Wilkins Co., Baltimore, 1964).

27. Scarpelli, E. M.: The lung, tracheal fluid, and lipid metabolism of the fetus. Pediatrics, *40:* 951 (1967).
28. Scarpelli, E. M.: The Surfactant System of the Lung (Lea & Febiger Publishers, Philadelphia, 1968).
29. Scarpelli, E. M.: Physiology and pathology of pulmonary surfactants. Triangle, *10:* 47 (1971).
30. Scarpelli, E. M.: Perinatal respiration. In: E. M. Scarpelli and P. A. M. Auld: Pulmonary Physiology of the Fetus, Newborn and Child (Lea & Febiger Publishers, Philadelphia, 1975).
31. Scarpelli, E. M.: Fetal pulmonary fluid. Rev. Perinatal Med., *1:* 49 (1976).
32. Scarpelli, E. M., Agasso, E. J., and Kikkawa, Y.: Demonstration of the significance of pulmonary surfactants at birth. Resp. Physiol., *12:* 110 (1971).
33. Scarpelli, E. M., Condorelli, S., and Cosmi, E. V.: Lamb fetal pulmonary fluid. I. Validation and significance of method for determination of volume and volume change. Pediat. Res., *9:* 190 (1975).
34. Scarpelli, E. M., Traver, D., and Clutario, B. C.: Personal observation.
35. Sobol, B., Boltex, G., Emirgil, C., and Gissen, H.: Gaseous diffusion from alveoli to pulmonary vessels of considerable size. Circ. Res., *13:* 71 (1963).
36. Strang, L. B.: Uptake of liquid from the lungs at the start of breathing. In: A. V. S. DeReuck and R. Porter: Development of the Lung (Little, Brown, and Company, Boston, 1967).
37. Taeusch, H. W., Jr., Carson, S. H., Wang, N. S., and Avery, M. E.: Heroin induction of lung maturation and growth retardation in fetal rabbits. J. Pediat., *82:* 869 (1973).
38. Thibeault, D. W., Wong, M. M., and Auld, P. A. M.: Thoracic gas volume changes in premature infants. Pediatrics, *40:* 403 (1967).
39. Functional residual capacity (FRC) was determined as the volume of fetal pulmonary fluid (FPF) measured *in utero* by the RISA dilution method (33). Thus the volume of air added during the first inflation to V_{max} was equal to the volume of FPF in the lung before inflation.
40. Since pressure is the dependent variable in our volume-pressure diagrams, we cannot define an "opening pressure" strictly. Nonetheless, an apparent opening pressure can be estimated from the shape of the curves shown in Figures 2 and 3.
41. The term "terminal lung unit(s)" (TLU) as used in this report includes both conducting structures, which we refer to as "airways," and terminal limiting structures, which we refer to as "periphery." "Airways" would be analogous to "transitional ducts" and "saccules"; and "periphery" would be analogous to "terminal saccules" as discussed by Hislop and Reid (15). We have not used the generally accepted nomenclature (15) because microscopic resolution in our preparations did not permit precise anatomic definition at the cellular level.
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44. Requests for reprints should be addressed to: Dr. Emile M. Scarpelli, Pulmonary Division, Department of Pediatrics, Albert Einstein College of Medicine, 1300 Morris Park Ave., New York, NY 10461 (USA).
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