Increased fragility of pulmonary capillaries in newborn rabbit

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Fu, Zhenxing, Gregory P. Heldt, and John B. West. Increased fragility of pulmonary capillaries in newborn rabbit. Am J Physiol Lung Cell Mol Physiol 284: L703–L709, 2003. First published October 25, 2002; 10.1152/ajplung.00276.2002.—The pulmonary capillaries of neonatal lungs are potentially vulnerable to stress failure because of the complex changes in the pulmonary circulation that occur at birth. We perfused fixed the lungs from nine anesthetized newborn rabbits at capillary transmural pressures (Ptm) of 5, 10, and 15 cmH2O. Normal microscopic appearances were seen at Ptm values of 5 ± 5, 10 ± 5, and 15 ± 5 cmH2O. Consistent with this, no disruptions of the alveolar epithelium were observed at Ptm values of 5 ± 5 cmH2O, but mean values of 0.11 and 1.22 breaks/mm epithelium were found at Ptm of 10 ± 5 and 15 ± 5 cmH2O, respectively (P < 0.05 for 5 vs. 10, 5, 10 cmH2O). These pressures are in striking contrast to those in the adult rabbit in which, by a similar procedure, a Ptm of 52.5 cmH2O is required before stress failure is consistently seen. We conclude that stress failure of pulmonary capillaries in newborn rabbit lungs can occur at Ptm values of less than one-third of those that are required in adult lungs.

neonatal lung; lung morphometry; capillary wall stress; stress failure

If the pulmonary capillaries of adult lungs are exposed to transmural pressures (Ptm) that exceed the normal maximal physiological values, ultrastructural changes occur in the walls, and a common result is the development of a high-permeability form of pulmonary edema (12, 15). This condition is known as stress failure because it is caused by the high circumferential stresses in the extremely thin capillary walls. There is evidence that the strength of the walls is attributable to the type IV collagen in the basement membranes of the alveolar epithelial and capillary endothelial cells (14), and on the thin side of the blood-gas barrier, these fused basement membranes make up the whole of the interstitial layer. In a recent study, we measured the thickness of the interstitium, epithelium, and endothelium from premature and term newborn rabbit lungs and compared these with adult lungs. A surprising finding was that the interstitium of the blood-gas barrier of newborn lungs was the thinnest among the three groups, and this suggested that the structure of the capillary wall might predispose to stress failure.

If true, this finding could have important potential clinical implications in the setting of neonatal lung disease. At birth, a complex series of events occur, including a rapid increase in the pulmonary blood flow from ~15% of the cardiac output before birth, to nearly the whole of the cardiac output. This is accomplished by a dramatic reduction in pulmonary vascular resistance brought about, in part, by the relief of hypoxia vasoconstriction, and also by inflation of the lung. These changes might be expected to greatly increase the Ptm of the pulmonary capillaries if not for the fact that the pulmonary artery pressure is simultaneously reduced by narrowing of the ductus arteriosus, although the hemodynamic events are complex, and the details are poorly understood. However, it is conceivable that the pulmonary capillaries might be transiently exposed to a high pressure, which could result in stress failure with leakage of plasma and red blood cells into the alveolar spaces where the plasma would inhibit the pulmonary surfactant (8). The end result might be very difficult to distinguish from the pathological picture seen in respiratory distress syndrome (RDS). Another possibility is that treatment of RDS by exogenous surfactant therapy could place the capillaries at risk by reducing the surface tension forces that may protect the capillaries under some conditions, e.g., when a high capillary Ptm causes them to bulge into the alveolar space (15). Alveolar hemorrhage after surfactant therapy has been described (10, 11). Thus it is possible that stress failure of pulmonary capillaries is an important element in the initiation of RDS, or it is possible that it can complicate surfactant therapy.

The present study describes for the first time the results of raising the capillary Ptm in newborn rabbits and studying the lung ultrastructure by electron microscopy. We report that the capillaries develop stress failure at far lower pressures than in the adult lung, suggesting that they are much more vulnerable to increased capillary pressure than has previously been appreciated.

MATERIALS AND METHODS

Animals

The protocol for the present study was approved by the Animal Subjects Committee at the University of California,
San Diego. Care and handling of rabbits were according to the guidelines of the National Institutes of Health.

The small size and the fragility of the neonatal lung made it technically very difficult to cannulate the pulmonary artery and left atrium and to carry out the perfusion fixation in situ at known vascular and airway pressures. Many preliminary studies were carried out to refine the technique, and the results from nine New Zealand White rabbit pups are reported here.

Anesthesia and Surgery

Newborn pups, 4–5 h after birth, were anesthetized by intraperitoneal injection of a mixture of nembutal (1 mg/kg) and pentobarbital sodium (10–15 mg/kg). A tracheostomy was performed with 10-cmH2O and the left atrial pressure held constant at 10 cmH2O, capillary arterial and venous pressure, and so was 10 cmH2O. It is possible that the distribution of pressures from pulmonary artery to vein is different in the newborn lung compared with the adult. However, the capillary Pd was not considered important.

Lung Perfusion Fixation

After the vessels were cannulated, the lungs were inflated to a pressure of 15 cmH2O, then deflated to 10 cmH2O positive pressure and kept at that pressure for the duration of the perfusion fixation. The pulmonary vasculature was perfused via the pulmonary artery with a saline/dextran mixture (11.06 NaCl g•L−1, 350 mosM; 3% T-70 dextran; 10 IU/ml heparin) that continued for ~4 min to wash out the blood. There was evidence that the perfusion was uniform in the adult because the whole lung became uniformly pale, and subsequent histological sections showed few red blood cells. The lungs were then fixed by perfusion for 10 min with buffered glutaraldehyde solution (phosphate-buffered 2.5% glutaraldehyde with 3% T-70 dextran; 500 mosM, pH 7.4). The reference level for vascular pressures was the middle of the thorax, and the hydrostatic pressure perfusion (inflow) was maintained within ±1 cmH2O of preset value by adjusting the height of the reservoir connected to the pulmonary artery. The outflow reservoir (connected to the left atrium via the left ventricle) was set 10 cm lower than the pulmonary arterial side. Both ventilators were ligated to prevent loss of perfusion fluid into the systemic circulation. This perfusion fixation technique was essentially identical to that which has been used in our laboratory for the past 10 yr to study stress failure of capillaries in adult rabbit lungs. The only difference is that we did not initially perfuse the lungs with blood, although they had been perfused with blood during life until just before the saline/dextran perfusion was begun.

Three animals were randomly assigned to each of the following groups: pulmonary artery pressure of 20, 25, and 30 cmH2O with the left atrial pressure held 10 cmH2O lower than the pulmonary artery pressure in each case. The pulmonary capillary pressure must lie between the pulmonary arterial and venous pressure, and so was 10–20, 15–25, and 20–30 cmH2O, respectively, in the three groups. Because alveolar pressure was held constant at 10 cmH2O, capillary Pd was 0–10, 5–15, and 10–20 cmH2O in the groups. In the adult pulmonary circulation, there is evidence that capillary pressure is about midway between arterial and venous pressure and that much of the pressure drop occurs in the capillary bed (1). Therefore, we have designated the capillary Pd in the three groups as 5 ± 5, 10 ± 5, and 15 ± 5 cmH2O. It is possible that the distribution of pressures from pulmonary artery to vein is different in the newborn lung compared with the adult. However, the capillary Pd must lie within the range given.

Tissue Sampling and Preparation

The lungs were removed following fixation and stored in buffered glutaraldehyde at 4°C. A single slab, ~0.3-cm-thick, was cut from the left lower lobe of each lung at approximately one-third the distance from the most caudal aspect. A vertical incision of small endothelial and epithelial disruptions was made to systematically select tissue blocks from vertical slices from each slab (6). The blocks were rinsed overnight in 0.1 M phosphate buffer (350 mosM, pH 7.4), postfixed for 2 hr in 1% osmium tetroxide in 0.125 M sodium cacodylate buffer (total osmolality 400 mosM, pH 7.4), dehydrated in increasing concentrations (70–100%) of ethanol, rinsed in propylene oxide, and embedded in Araldite. For light microscopic examination, sections (1 μm) were cut from each of two blocks with an LKB Ultratome III and stained with 0.1% toluidine blue aqueous solution. For electron microscopy, ultrathin sections (50–70 nm) were processed for contrast with uranyl acetate and bismuth subnitrate (7) and were examined with a Zeiss electron microscope. This procedure is the same as we have used for many years for studying adult rabbit lungs.

Morphometric Analysis

Electron microscopy. For each rabbit lung, a total of 60 electron micrographs were taken (30 micrographs taken by random systematic sampling from a single ultrathin section from each of 2 blocks). A micrograph of a carbon grating replica (E. F. Fullam, Schenectady, NY) was taken on each film for calibration.

All the negatives of electron micrographs were scanned and saved on a compact disc. An IBM personal computer loaded with Matlab 5.3 was used to determine the frequency of endothelial and epithelial disruptions and the thickness of the endothelial, epithelial, and interstitial layers of the blood-gas barrier. The resolution on the computer screen was not always sufficient to distinguish the basement membrane. Therefore, prints of each negative were available for positive identification of structures on the computer screen, as needed, during measurement. This allowed an unequivocal identification of small endothelial and epithelial disruptions as well as the presence (or absence) of basement membrane at all sites of rupture, as was the case with our previous studies (2, 12).

The following measurements were performed in each field of view. The frequency of disruptions of the blood-gas barrier was quantified as the number of breaks per unit of endothelial and epithelial boundary length in the sections. This was achieved by tracing the contour of capillary (inner endothelial) and alveolar (outer epithelial) boundary segments in each field of view and by counting the number of endothelial and epithelial disruptions. The presence and absence of a basement membrane at each disruption site (endothelial and epithelial) as well as the presence of red blood cells (at endothelial break sites) were recorded. The presence and extent of interstitial edema were assessed by measuring the thickness (profile width) of each layer of the blood-gas barrier (endothelium, interstitium, and epithelium). One to five sites were systematically sampled in each micrograph with the
result that 209–241 blood-gas barrier sites were measured for thickness in each animal.

Statistics

Data are expressed as means ± SE. The equation for the SE of ratio (4) was computed from the estimates of the number of breaks per unit boundary length. Data from all micrographs (n = 60) from a single sample were pooled for these estimates, so the computed SE represents the variability between micrographs at that site. The SE of the estimates of break length and blood-gas barrier thickness indicates the variability between individual measurements. Group means were compared by Student’s t-test and analysis of variance. Differences were taken as significant for \( P < 0.05 \).

RESULTS

Macroscopic Findings and Light Microscopy

In all the lungs in which the capillaries were exposed to \( P_{tm} \) values between 5 ± 5 and 15 ± 5 cmH₂O, no obvious damage to the lung surface was observed, although the lungs with capillaries exposed to 15 ± 5 cmH₂O \( P_{tm} \) looked more swollen than those for \( P_{tm} \) values of 5 ± 5 and 10 ± 5 cmH₂O. Frothy fluid in the tracheal cannula was seen in the lungs perfused at \( P_{tm} \) of 15 ± 5 cmH₂O but not in the lungs of 5 ± 5 and 10 ± 5 cmH₂O \( P_{tm} \). Figure 1, A–C, shows representative light micrographs of the lung parenchyma at each perfusion pressure. The capillaries appeared more distended as the \( P_{tm} \) was increased from 5 ± 5 to 15 ± 5 cmH₂O. In these newborn lungs, there were many interstitial cells between double capillary layers, especially at the junctions of these double layers (Fig. 1A). At a \( P_{tm} \) of 5 ± 5 cmH₂O, no edema was observed between interstitial cells in the capillary wall (Fig. 1A). By contrast, at a \( P_{tm} \) of 15 ± 5 cmH₂O, the lung parenchyma showed pockets of edema in the interstitial space, and the normal structure of the interstitium had disappeared (Fig. 1C).

Electron Microscopic Findings

General appearance. Figure 2 shows the ultrastructural appearance of pulmonary capillaries perfusion fixed at the three \( P_{tm} \) levels. At a \( P_{tm} \) of 5 ± 5 cmH₂O, the integrity of the parenchyma was well preserved with normal separation of the endothelial cells, epithelial cells, and collagen fibers (Fig. 2A), and there was no clear evidence of edema in the interstitial space. When the \( P_{tm} \) was increased to 10 ± 5 cmH₂O, widening between the endothelium and epithelium was observed, especially at the junctions of capillaries, indicating that edema fluid had accumulated in the interstitial space (Fig. 2B). When the \( P_{tm} \) reached 15 ± 5 cmH₂O, the structure of the interstitium between double capillaries was markedly altered, with larger amounts of edema fluid between interstitial cells and the capillary walls. The endothelium and epithelium of the thin portion of the blood-gas barrier were often seen separated from each other, and breaks of both layers were observed (Fig. 2, C and D).

Endothelial discontinuities. The average frequencies and lengths of disruptions of the capillary endothelium in newborn rabbit lungs perfusion fixed at each \( P_{tm} \) are shown in Table 1 and plotted in Fig. 3. Only a few endothelial breaks were found in one animal (607-8) among the three animals in the group of 5 ± 5 cmH₂O \( P_{tm} \). The average frequency of the disruptions increased as the \( P_{tm} \) increased from 10 ± 5 cmH₂O to 15 ± 5 cmH₂O. In most instances, the basement membrane was seen to be intact in the plane of the section figure.
at the site of the endothelial breaks. At a $P_{tm}$ of $10 \pm 5$ cmH$_2$O, 100% of the endothelial breaks had an intact basement membrane, and the value was 97% at the $P_{tm}$ of $15 \pm 5$ cmH$_2$O.

The average lengths of all endothelial breaks for each $P_{tm}$ are given in Table 1. There was no significant difference in the average endothelial break length among three groups, although the average length was smaller at a $P_{tm}$ of $5 \pm 5$ cmH$_2$O than in the $10 \pm 5$- and $15 \pm 5$-cmH$_2$O $P_{tm}$ groups.

**Epithelial discontinuities.** No epithelial breaks occurred in the group of $5 \pm 5$ cmH$_2$O $P_{tm}$, and only one break was found in one of three animals in the group of $10 \pm 5$ cmH$_2$O $P_{tm}$, as shown in Table 1 and Fig. 3. The mean number of epithelial breaks in the group of $15 \pm 5$ cmH$_2$O $P_{tm}$ was $1.22 \pm 0.06$ ($P < 0.05$ compared with $P_{tm}$ of $5 \pm 5$ cmH$_2$O). Eighty percent of the breaks had an intact basement membrane underneath. Occasionally, the epithelial layer apparently disintegrated, with small fragments of epithelium remaining over either

![Fig. 2. Electron micrographs of blood-gas barrier in newborn rabbit lungs perfusion fixed at $P_{tm}$ values of $5 \pm 5$ (A), $10 \pm 5$ (B), and $15 \pm 5$ (C and D) cmH$_2$O. A: normal capillary ultrastructure. B: note the edema fluid starting to accumulate in the interstitial space (star). C and D: disruption of the capillary endothelium (closed arrows) and epithelium (open arrow). a, Alveolus; c, capillary.](image)

<table>
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<th>Transmural Pressure, cmH$_2$O</th>
<th>Animal No.</th>
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<th>Epithelium</th>
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<td>Breaks/mm</td>
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<td>0.96 $\pm$ 0.47</td>
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<tr>
<td></td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>6.55 $\pm$ 4.68</td>
<td>0.92 $\pm$ 0.17</td>
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Values are means $\pm$ SE. *In this animal, only 1 epithelial break was seen.
an intact or broken basement membrane as shown in Fig. 2D (open arrow).

The average lengths of all epithelial breaks for each Ptm are shown in Table 1. The epithelial breaks tended to be longer than the endothelial breaks at 15 ± 5 cmH2O Ptm, but the difference is not statistically significant.

**Thickness of the blood-gas barrier.** Figure 4 shows the average thickness of each of the layers of the blood-gas barrier and total barrier thickness. The thickness of the interstitial space increased with the rise of the Ptm as a result of edema (P < 0.01 for 5 ± 5 vs. 15 ± 5 cmH2O). However, the thickness of the endothelial layer did not change, whereas the thickness of the epithelial layer tended to decrease, although the change was not statistically significant.

Possibly, this can be explained by stretching of the layer at the high pressures.

**DISCUSSION**

**Stress Failure of Pulmonary Capillaries Occurs With Lower Ptm in Newborn Than in Adult Lung**

The most important finding in this study is that the blood-gas barrier in the newborn rabbit was much more fragile than in the adult when the capillary Ptm was raised. This fragility is shown by the fact that frothy edema fluid was seen in the airways at the surprisingly low Ptm value of 15 ± 5 cmH2O and is confirmed by the microscopic evidence of stress failure. In our previous study of stress failure in the adult rabbit (12), we showed that a capillary Ptm of 52.5 cmH2O was required before discontinuities were consistently seen in the endothelial or epithelial layers of the blood-gas barrier (Fig. 5).

It was, therefore, very surprising to find that in all three newborn lungs perfused with a capillary Ptm of only 15 ± 5 cmH2O, massive frothy edema fluid was observed coming out of the tracheal cannula. As Figs. 3 and 5 show, this frank alveolar edema was associated with an average of 6.6 breaks/mm in the endothelium and 1.2 breaks/mm in the epithelium. A small number of breaks were also seen in the animals in which the capillary Ptm was only 10 ± 5 cmH2O, but there were fewer than 1 break per/mm for endothelium and only ∼0.1 breaks/mm for epithelium. Two of the three animals in this group showed no epithelial breaks.

**Mechanism for the Fragility of Capillaries in Newborn Lungs**

There is evidence that the mechanical strength of the blood-gas barrier comes from the basement membranes in the extracellular matrix (14). The evidence includes the fact that on the thin side of the blood-gas barrier in the adult lung, the extracellular matrix is...
composed only of the two fused basement membranes of the capillary endothelial and alveolar epithelial layers. Therefore, at this site, other components of the extracellular matrix, such as type I collagen, cannot play a role. Other evidence of the importance of the basement membranes includes the fact that when stress failure occurs with breaks in the capillary endothelial or alveolar epithelial layers, the basement membranes frequently remain intact (12). In addition, the few measurements that have been made on the ultimate tensile strength of basement membrane indicate that this is very large, presumably because of the presence of type IV collagen (14). Further evidence is that when isolated rabbit renal tubules consisting only of a basement membrane and a layer of epithelial cells are inflated by increasing the $P_{tm}$, the pressure-diameter behavior is the same regardless of whether or not the epithelial layer is present (13). In addition, glomerular capillaries, which routinely withstand a much higher $P_{tm}$ than pulmonary capillaries, have a much thicker basement membrane. Finally, in patients who have an increased pulmonary capillary pressure over a long period, such as those with mitral stenosis, the basement membranes of the pulmonary capillaries are thickened.

It is not technically possible to measure the thickness of the basement membranes alone in the capillaries of the newborn and adult lung. However, in a previous study, we measured the thickness of the capillary endothelial, alveolar epithelial, and extracellular matrix layers of the blood-gas barrier in newborn and adult rabbits and also in preterm lungs. We were surprised to find that many measurements of the thickness of the extracellular matrix in the full-term newborn rabbit were much less than those in either the adult or the preterm pups. Although this does not prove that the extraordinary fragility of the pulmonary capillaries in newborn lungs can be attributed to the thinner extracellular matrix, it is consistent with this theory. It is also known that in the newborn lung, there is rapid turnover of the extracellular matrix proteins, and this might contribute to the reduced mechanical strength.

**Comparison of the Pattern of Stress Failure in Newborn and Adult Lungs**

It is interesting to compare the various features of stress failure in newborn and adult lungs. Figure 3 shows that in the newborn lung, the number of breaks in the capillary endothelial layer generally exceeded the number in the alveolar epithelial layer, particularly at the highest $P_{tm}$ of 15 ± 5 cmH$_2$O. This plot has some similarities to the distribution of breaks in the adult lung, as described by Tsukimoto et al. (12), and is shown in Fig. 5. In the adult, the number of endothelial breaks was almost double the number of epithelial breaks at the highest $P_{tm}$, which in this case was 72.5 cmH$_2$O. However, interestingly, the number of endothelial and epithelial breaks was approximately the same at the lower pressures of 32.5 and 52.5 cmH$_2$O in contrast to the pattern seen at a $P_{tm}$ of 10 ± 5 cmH$_2$O in the newborn animals.

It is also interesting that the number of breaks, both in the endothelium and epithelium, that was associated with an intact basement membrane in the plane of the section was greater in the newborn than in the adult lungs. For example, 100% of the endothelial breaks had an intact basement membrane at a $P_{tm}$ of 10 ± 5 cmH$_2$O, and the value was 97% at a $P_{tm}$ of 15 ± 5 cmH$_2$O. For epithelial breaks at a $P_{tm}$ of 15 ± 5 cmH$_2$O, 80% had an intact basement membrane. These results can be contrasted with those in the adult lung in which the number of endothelial breaks associated with an intact basement membrane was only 51% for a $P_{tm}$ of 52.5 cmH$_2$O and 57% for a $P_{tm}$ of 72.5 cmH$_2$O. The proportion of epithelial breaks associated with an intact basement membrane was similar, the percentages being 56% for a $P_{tm}$ of 52.5 cmH$_2$O and 61% for a $P_{tm}$ of 72.5 cmH$_2$O. Apparently, the capillary endothelial and alveolar epithelial layers tend to be more easily disrupted in newborn lungs compared with the associated basement membranes.

Another interesting point is that the lengths of the endothelial breaks tended to be greater than those of the epithelial breaks in the newborn lungs except at the highest $P_{tm}$ of 15 ± 5 cmH$_2$O. However, as Fig. 6 shows, a P$_{tm}$ at which 50% of the endothelial breaks occurred at a $P_{tm}$ of 15 ± 5 cmH$_2$O. In another study of 31 unanesthetized lambs from 4 to 10 days of age, the mean pulmonary artery pressure was 19 mmHg (9). These pressures correspond to a mean of 45cmH$_2$O.

There is no direct information about the pressure drop along the pulmonary circulation from pulmonary artery to capillaries to pulmonary veins in newborns. However, in immature lambs, most of the pressure drop has been shown to be in the lung and small pulmonary arteries (5), and, presumably, the arterial vasoconstriction is partly responsible for limiting the proportion of the cardiac output that goes through the lung to ~15%. Most of the circulation bypasses the lung through the ductus arteriosus. The high degree of arterial vasoconstriction also protects the pulmonary capillaries from the high pulmonary artery pressure, which is the same as that in the aorta in the fetus.

There is some evidence that in the adult lung, the pulmonary capillary pressure is about halfway between pulmonary arterial and venous pressures (1), and a similar distribution of pressures has been de-
scribed in the immature fetal lamb under some conditions (5). If this were true of the newborn lung, the present study suggests that the pulmonary capillaries would be at risk. If we take the pulmonary venous pressure to be 3 mmHg (4 cmH2O), as reported by Bland and McMillan (3), and use the value of 25 cmH2O for mean pulmonary artery pressure, the capillary pressure would be approximately halfway between 25 and 4 cmH2O or ~14.5 cmH2O. However, as Fig. 3 shows, marked stress failure of pulmonary capillaries occurs at a Ptm of 15 ± 5 cmH2O. Presumably, the distribution of pressures in the pulmonary circulation in the newborn lung is such that the pulmonary capillary pressure is maintained at a lower value by some residual vasoconstriction of the pulmonary arteries. However, the safety factor appears to be low. Our findings are consistent with the observed alveolar hemorrhage seen in immature lamb lungs at a Ptm of ~19 cmH2O (5).

In conclusion, in this first study relating the frequency of stress failure of pulmonary capillaries to the capillary Ptm in newborn rabbits, the capillaries appear to be extraordinarily vulnerable. Obvious stress failure of the blood-gas barrier with breaks in both the capillary endothelial and alveolar epithelial layers was seen at a capillary Ptm of only 15 ± 5 cmH2O. Because the mean pulmonary arterial pressure is apparently of the order of 25 cmH2O, the safety factor is apparently very low. Furthermore, because of the dramatic changes that occur in the pulmonary circulation at birth, in which there is a sudden increase in the proportion of the cardiac output going through the lungs, and a decrease in the pulmonary artery pressure as a result of closure of the ductus arteriosus, the possibility of transient exposure of the pulmonary capillaries to high pressures appears to be very real. If this occurs, the net result would be stress failure of the capillaries with hemorrhagic pulmonary edema, inhibition of the alveolar surfactant by the blood plasma, and a pattern very like the classic respiratory distress of the newborn. We suggest that this mechanism may contribute to this disease in newborn humans.

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