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LYMPHODYNAMICS IN THE FETUS AND NEWBORN

C. Bellini, F. Boccardo, E. Bonioli, C. Campisi

Servizio di Patologia Neonatale, Dipartimento di Pediatria (CB,EB), and Dipartimento di Chirurgia (FB,CC), Discipline Chirurgiche Morfologiche e Metodologie Integrate (DiCMI), U.O.S. Dipartimentale di Microchirurgia dei Linfatici, Azienda Ospedale-Università San Martino, Università di Genova, Istituto G. Gaslini, Genova, Italy

ABSTRACT

Body fluid is distributed among three major fluid spaces: plasma, interstitial fluid, and intracellular fluid. The distribution of fluid in each of these compartments is dramatically different in the fetus and newborn compared to the adult. In addition, the amniotic fluid that surrounds the fetus may also be considered an extension of the extracellular space of the fetus. The purpose of this review is to discuss the complex mechanism that regulates volume in the fetus and newborn as well as the regulation of fluid distribution between the plasma and interstitial fluid, while placing special emphasis on the role the lymphatic system plays in mediating and maintaining this distribution.

Keywords: lymphodynamics, lymphatic physiology, fetus, neonate, extracellular volume regulation, lung lymph

Distribution of Fluids in the Fetus and Neonate

Water is the most plentiful component in the human body. Total body water (TBW) as a percentage of body weight varies with age with values of approximately 95% of the total body weight in early gestation, 75% at term, and 62% by nine months of age (1). TBW is divided into two main compartments — intracellular fluid (ICF) and extracellular fluid (ECF) — and in the fetus and in the newborn ECF is greater than ICF. As gestation proceeds and into adulthood, the proportion of body water in the ECF drops while the proportion in the ICF increases slightly (1) (*Fig. 1*).

The ECF is further distributed into the plasma (in the intravascular space) and into the interstitial fluid space. The plasma volume per unit body weight does not change at different fetal ages, which suggests that the reduction in ECF is mainly due to the loss of interstitial fluid. *Fig. 2* displays TBW, ICF, and ECF in normal at-term newborns as a percentage of body weight and the distribution of ECF components as a percentage of TBW. Little is known about which factors regulate the distribution of fluid between plasma and interstitial spaces in the normal human fetus. In late-gestation fetal sheep, the best estimate for plasma volume is 76 ml/kg. Interstitial volume has been estimated to average three times this volume, or 235 to 240 ml/kg of body weight (2). It should be pointed out that the ratio of interstitial fluid volume to plasma volume in the sheep fetus (3:1) is similar to what is found in adult sheep. This ratio can be misleading because roughly 30% of the circulating plasma in the fetus is located outside the fetal body, i.e., in the umbilical cord and placenta. When the ratio of interstitial fluid volume to plasma volume is adjusted for this, it becomes 4.4:1 in the fetus, thereby indicating that the interstitial space

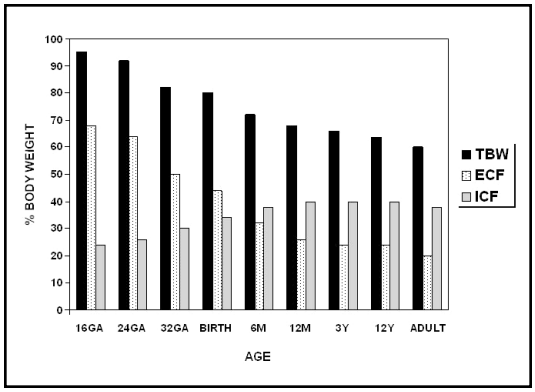

Fig. 1. Total body water (TBW) content, extracellular fluid (ECF), and intracellular fluid (ICF) distributions as percentage of body weight during fetal development, neonatal period, and adulthood. (GA: gestational age; M: months; Y: years) [Adapted from (27) and (2)].

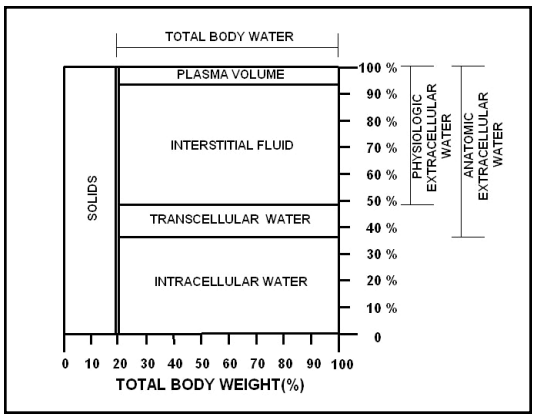

Fig. 2. Total body water as percentage of body weight and body water compartments as percentage of total in normal at-term newborns. The anatomic extracellular water (ECW) compartment includes the physiologic extracellular water (plasma value and interstitial fluid) and the transcellular water compartments. [Adapted from (27) and (2)].

of the fetus is expanded as compared to the adult. It is estimated that plasma volume in humans is approximately 40 to 60 ml/kg, while extracellular fluid averages 397 ml/kg. The difference between these numbers (350 ml/kg) represents the volume of interstitial fluid. The interstitial to plasma volume ratio calculated on the basis of these numbers is 7.6:1 (*Table 1*) (1,2). At term, approximately 30% of body weight is made up of intracellular water while 45% is made up of extracellular water (1).

Next, we will briefly discuss known changes that take place during intrauterine development, during labor and delivery, and in the post-natal period as well as special fluid compartments.

Changes During Intrauterine Development

In early gestation, body composition is characterized by a high proportion of TBW and large extracellular compartments. As gestation progresses, the rapid cellular growth and the increase in body solids and fat stores lead to a gradual decrease in TBW content and extracellular water volume, while the intracellular fluid compartment increases. In a 16-week fetus, TBW represents approximately 94% of body weight (one-third intracellular and two-thirds extracellular, with the majority of the latter being distributed in the interstitium). TBW makes up approximately 80% of the body weight (almost 40% of which is intracellular) in at-term neonates (*Fig. 2*).

Changes During Labor and Delivery

Labor and delivery cause acute changes in TBW and its distribution. Arterial blood pressure increases due to catecholamine, vasopressin, and cortisol increased plasma levels. Thus, the translocation of blood from the placenta to the fetus, together with intrapartum hypoxia, generate a shift of fluid from the intravascular to the interstitial compartment. In turn, this generates a reduction of approximately 25% in circulating plasma volume in the human fetus during labor and delivery. The post-natal increase in oxygenation, as well as the changes in the vasoactive hormonal production, then restore the integrity of the capillary barrier, and the fluid in the intravascular space is reabsorbed.

TABLE 1
Estimated Values of Plasma Volume, Blood Volume, Red Blood Cell Volume, and Total Extracellular Fluid (ECF) in the Human At-term Neonate

Plasma volume	41-62 ml/kg
Blood volume	78-100 ml/kg
Red blood cell volume	32-41 ml/kg
Total ECF volume	400-500 ml/kg
Interstitial fluid volume (ECF minus plasma volume)	~ 350 ml/kg
Ratio interstitial fluid: plasma volume	~ 8:1

Changes in the Post-Natal Period

During the early transitional period, the healthy newborn loses weight. It is generally accepted that this post-natal weight loss is mainly due to the contraction of the expanded ECF compartment and that it approximates the total body fluid loss. Water loss from the intracellular space may also contribute to the physiologic weight loss, especially when rapid changes occur in serum osmolality, which can be seen in extremely low-birth-weight infants with increased transependimal water loss (3,4).

It is beyond the scope of this review to discuss hormonal and renal regulation of extracellular fluid volume in neonates, but other physiological processes such as the renin-angiotensin system, sympathetic nervous system and adrenal medulla, anti-diuretic hormone, atrial natriuretic peptide, baroreceptor function, and renal blood flow, glomerular filtration rate, concentration and dilution of the urine will also affect ECF (1).

Special Fluid Compartments

There are additional fluid spaces, such as the lungs and the stomach, that must be taken into consideration in order to understand how plasma and interstitial volumes are regulated during the perinatal period.

Prior to birth, the developing lungs are filled with fluid and not with gas. Fluid is formed by the active secretion of chloride ions into the alveolar spaces, which results in the progressive accumulation of fluid in the lungs as gestation progresses. The secretion of lung fluid far exceeds what is needed for volume expansion of the lungs, thus the excess lung fluid exits through the trachea. In fetal lambs, the tracheal flow rate averages 4.4 ml/kg per hour during the latter half of gestation, and over a 24-hour period, this volume represents approximately 10% to 15% of body weight. The lung fluid in at-term lambs averages 45 ml/kg of body weight, or slightly more than one half of the plasma volume. It is not known how easily fetal lung fluid can be transferred to the circulation (2, and references therein).The stomach may also be a major fluid reservoir in both the fetus and in the neonate. Episodic swallowing may involve as much as 100 to 200 ml, approximately 3% to 5% of body weight.

We will now focus on lymph and lymph flow in the fetus and newborn, and on the role of lymphatics in lung fluid balance before and after birth.

Lymph and Lymph Flow

The volume of fluid within the lymphatic system is small and averages only 1 ml/kg body weight in adult dogs as estimated from lymph flow dynamics (2, and references

therein). Lymphatic flow has never been measured in the human fetus or neonate and it is reasonable to speculate that there are developmental changes in lymphatic volume. Studies on other species have shown higher flow rates in the fetus and newborn than in the adult. It has long been known that lymph flow from the subcutaneous tissue in anesthetized puppies is about twice what is observed in adult dogs, and studies on anesthetized newborn lambs and puppies demonstrated that lymph flow from the lungs is higher than in adult counterparts (2). These observations support the theory that both the local and the whole body lymph flow rates, in relation to body weight, are significantly greater in the neonatal period than later in life. The increased flow may reflect the higher ratio of interstitial fluid volume to plasma volume in the fetus and neonate compared to the adult.

In the fetus, lymph flow rates relative to weight appear to be greater than in the newborn. Few studies are available in this area (2, and references therein), and furthermore, they are impaired by confounding factors, in particular the diameter of the catheters that are used to evaluate thoracic duct flow. In fact, when a long, small-diameter catheter was used (5), fetal left thoracic duct flow averaged approximately 0.08 ml/minute per kg, which is substantially comparable with adult flow rate. However, when low-resistance catheters were used, thoracic duct lymph flow averaged 0.25 ml/minute per kg (6). Another important point that must be taken into consideration is that these studies were carried out on anesthetized animals, and we must remember that anesthesia has been shown to reduce lymph flow rates (6). Despite these latter considerations, we can conclude that basal lymph flow rates in the fetus are higher than in the newborn, and that lymph flow rates in the newborn are higher than in the adult. Thus, a possible consequence of reduced lymph flow in the fetus is fluid retention and the gradual formation of generalized fetal tissue edema, i.e., hydrops fetalis (7). It is well known (8) that the lymphatic system must propel lymph against venous pressure in order to return into the blood circulation. Therefore, the normal outflow pressure for the lymphatic system in the great veins at the base of the neck is venous pressure. Little else is known about the fetal or neonatal lymphatic system except what has been observed in a few studies carried out on fetal and newborn sheep. It is now becoming clear that there are major developmental differences in the functional ability of the lymphatic system to pump fluid from the interstitial spaces back into circulation during fetal life (7, 9). The main difference is related to the various effects that venous pressure has on lymph flow during prenatal and post-natal life, as well as later on in life.

Studies on the effects of outflow pressure and vascular volume loading on thoracic duct lymph flow in adult sheep (10) showed that there is a plateau where thoracic duct lymph flow rate is independent of outflow pressure. Large increases in venous pressure are required to totally block thoracic duct lymph flow. Whenever outflow pressure was negative in the fetus (11,12), lymph flow was independent of outflow pressure, averaging at 0.66±0.05 ml/min. When outflow pressure of the left thoracic duct increased to above zero, lymph flow decreased linearly with outflow pressure, and flow stopped at an outflow pressure of 11.5±0.6 mm Hg. These observations showed that normal venous pressure in the fetus does not appear to be an impediment to basal lymph flow, and that any increase in venous pressure reduces the lymph flow rate. In the adult, venous pressure has to be significantly higher than normal to obtain a decrease in lymph flow and an increase in outflow pressure. Lymph flow stops in the fetus when venous pressure rises to 16 mm Hg, while thoracic duct lymph flow stops at 26 mm Hg in adult sheep (*Table 2*).

Lung Lymph Flow

In the normal lung, the rate of lung

TABLE 2
Relationship of Left Thoracic Duct Lymph Flow to Rising Outflow Pressure in Unanesthetized Fetal and Adult Sheep

Left thoracic duct lymph flow (ml/day/kg body wt)		Outflow pressure (mm Hg)	
Fetus	Adult	Fetus	Adult
220	55	-20	-20
220	55	-10	-10
220	55	0	0
110	50	10	10
50	20	14	20
0	0	16	26

TABLE 3
Composition of Simultaneously Sampled Lung Liquid, Plasma, Lung Lymph, and Amniotic Fluid from Fetal Sheep of 125-147 Days Gestation

	Na^+ (mM)	K^+ (mM)	Cl^- (mM)	HCO_3^- (mM)	Protein (g/dl)
Lung liquid	150	6.3	157	2.8	0.03
Plasma	150	4.8	107	24	4.09
Lung lymph	147	4.8	107	25	3.27
Amniotic liquid	113	7.6	87	19	0.10

lymph flow is equal to the net rate of fluid filtration and, thus, water does not accumulate in the lung (13). Although fluid may be actively pumped by lymphatics against a pressure gradient, studies show that this ability is limited and that there is an inverse variation in lung lymph flow depending on the outflow pressure (pressure in the superior vena cava). The ability of the lymphatics to pump against an outflow pressure is impaired in the fetus and newborn. Thoracic duct lymph flow in fetal lambs ceases at an outflow pressure of roughly 15 mm Hg (14). On the basis of studies performed in 1941 (15), it was assumed that inhaled amniotic liquid was the source of fetal lung fluid. However, the original report by Potter and Bohlender (15), whose conclusions were confirmed by later experiments, proved that the source of fetal lung liquid was the lung itself. Analysis of the composition of the lung liquid (*Table 3*) demonstrated that it was a specialized secretion of the fetal lung. The developing distal lung epithelium displays an evolving liquid transport phenotype, and the critical point is the balance between the Cl^- ion active secretion and Na^+ ion absorption. Cl^- ion active driven liquid secretion is predominant during fetal life. Lung liquid is secreted against a resistance provided by the larynx and nasopharynx while the vocal cords act as a one-way valve (16). A luminal pressure of 2-3 torr above amniotic fluid pressure is generated, and it is the main lung

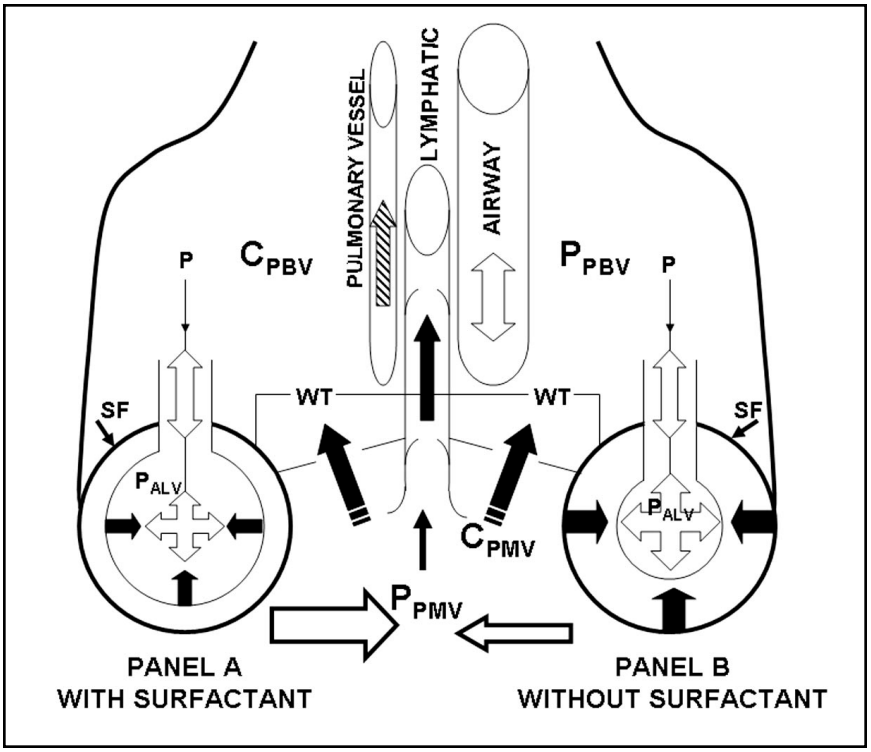

Fig. 3. Effects of lung ventilation on lymphatic edema clearance from the lung. Laplace relationship and the effects of surfactant film and alveolar radius are taken into consideration. List of abbreviations: SF: surfactant film. WT: wall or surface tension. P: pneumatic pressure. P_{ALV}: intraalveolar pressure. P_{pmv}: perimicrovascular pressure. C_{pmv}: perimicrovascular compliance. P_{pbv}: peribronchovascular pressure. C_{pbv}: peribronchovascular compliance.

When breathing, inspiration compresses a low-compliance perimicrovascular space near the alveolar vessels and enlarges the interstitial space surrounding the extra-alveolar vessels, airways, and conduit lymphatics. Breathing phasically increases the upstream pressure for lymphatic drainage, while simultaneously decreasing downstream pressure and lymphatic resistance. The accumulation of edema fluid increases the peribronchovascular interstitial pressure. Increasing lung volume during breathing leads to phasic lymphatic compression simultaneously with the perimicrovascular interstitial space. Lymphatic valves keep the lymph flow unidirectional. The phasic circumferential and longitudinal stretching of lymphatics during each breath may be triggered by an active lymphatic contraction. The separate effects of tidal volume and frequency (hyperpnea) on lung lymph flow are still poorly understood.

In the newborn, a further important factor comes into play, i.e., the lung maturation. The main contributor to newborn lung elastic recoil is surface tension, which is closely related to the presence of surfactant. The pressure required to counteract the tendency of the bronchioles and for the terminal air space to collapse is described by the well-known Laplace relationship $P = 2\ ST / r$. Since the air-liquid interface is only located on one side of the terminal lung in the newborn, it would be more appropriate to write the relationship as $P = ST / r$, where P is the pressure that is needed to stabilize the system, ST is the surface tension, and r is the alveolar radius. Thus, the larger the alveolar radius, the less pressure is needed to hold the alveolus open or to expand it further. In the figure, the various sizes of the open arrows within the alveolus on left (with surfactant) and on right (without surfactant) highlight the varying intraalveolar pressure that is needed to counteract the tendency of the alveolus to collapse (solid arrows). The pressure is directly proportional to the wall or surface tension and inversely proportional to the radius size. In conclusion, as compared to the adult, the at birth newborn needs to drain more lung liquid through lymphatics. Infants with respiratory distress syndrome caused by surfactant reduction must generate high negative intrapleural pressure to obtain alveolar expansion. If the infant fails to achieve expansion and stabilization of the distal airways and alveoli, then the compression of low-compliance perimicrovascular space near the alveolar vessels and enlargement of the interstitial space surrounding extraalveolar vessels, airways, and conduit lymphatics may be insufficient to obtain optimal liquid drainage through the lymph vessels [modified from (21) and (28)].

expanding force (17). Na^+ absorption activity increases toward the end of gestation and switches to the at-birth and beyond absorptive phenotype. Although the secretion of liquid into the lung lumen is critical for lung growth, this liquid must be removed at birth to allow the newborn to breathe air. Lung liquid removal begins immediately after birth and is normally complete within the first 2 hours of life (18). Labor has a great importance in regulating the absorption of lung liquid (19). Blood vascular and lymphatic systems are involved in this process, and in particular the size of lymphatics has been estimated to vary between 11% for animals during labor and 50% for animals not during labor (18). Lung ventilation is extremely important in regulating lung lymph flow in the newborn (20).

Recent studies (21) demonstrated that both increases and decreases in ventilation caused significant and rapid changes in lung lymph flow, which were not related to changes in lung weight. The variation in lung lymph flow after the increase in tidal volume was transient and not correlated to lung weight, suggesting that ventilation affects lung lymph flow through some direct effects on the edema filled interstitium and lymphatic vessels. On the other hand, a decrease in tidal volume resulted in decreased lung lymph flow, suggesting that decreased tidal volume might act by increasing the downstream lymphatic resistance (21,22).

Effect of Ventilation on Lymphatic Edema Clearance from the Lung

It has been speculated that there are three different physiologic mechanisms that may explain the relationship between ventilation and lung lymph flow. *Fig. 3* shows the physiologic pattern (see details in the legend). Both increases and decreases in ventilation cause significant, rapid changes in lymph flow. Inspiration compresses the low-compliance perivascular space surrounding the extravascular vessels, airways, and conduit lymphatics (20,21,23). The inspiration phasically increases the upstream pressure on lymphatic drainage while simultaneously decreasing downstream pressure and lymphatic resistance by dilating conduit lymphatic vessels. The accumulation of edema fluid increases the peribronchovascular interstitial pressure (24). The increased lung volume phasically compresses both the conduit lymphatics and the perimicrovascular interstitial space at the same time. With regards to the direction of the pressure gradient between the two interstitial compartments, lymph flow remains unidirectional due to the presence of lymphatic valves. The phasic circumferential and longitudinal stretching of interstitial lymphatics occurring with each breath may trigger an active lymphatic contraction. It has been hypothesized that the increase in lung lymph flow that is associated with the increase in volume is the result of a volume-induced increase in the rate of fluid filtration across extra-alveolar vessels (21,22,25).

CONCLUSION

Extracellular fluid volume changes markedly during endo-uterine life and then in the neonatal period. Hormonal, renal, and cardiovascular mechanisms are the main factors that strongly influence the regulation of extracellular fluid volume in the fetus and neonate (18). Very little is known about lymphatic function during the fetal or the neonatal period, and there is a great deal more to learn about its regulation. In conclusion, we can point to some peculiar conditions that can be observed early in life, i.e., lymphatics must cope with increased interstitial fluid, fetal lymph flow is five times greater than in adults, flow depends on outflow pressure, a slight increase in central venous pressure results in a dramatic decrease in lymph flow, and lastly, lung liquid removal is significantly linked to lung lymph flow and lung tidal volume.

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Carlo Bellini, MD, PhD
Dipartimento di Pediatria
Università di Genova
Istituto G. Gaslini,
Largo G. Gaslini, 5
16147 Genova, Italy
Tel: +39 10 5636762
Fax: +39 10 3770675
Email: carlobellini@ospedale-gaslini.ge.it