Janaki Medical College Journal of Medical Sciences (2024); Vol.12 (3):108-122

JMCJMS

Review Article

Pulmonary Surfactant in Health and Disease: An Overview

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ABSTRACT

Surfactant is a complex mixture of phospholipids, mainly dipalmitoylphosphatidylcholine (DPCC) and surfactant proteins (SP); SP-A, SP-B, SP-C, and SP-D. DPCC plays a crucial role in lowering the surface tension, while SPs provide immunity against invading pathogens. SPs also enhance the activity of phospholipids, aiding in the adsorption and spread of surfactants all over the alveolar surface. Surfactant production starts as early as 24 weeks of gestation in humans and peaks at about 36-38 weeks. The generation and secretion of lung surfactants are tightly regulated processes. Surfactant is synthesized by type II alveolar cells and stored in lamellar bodies. Following stimulation, these lamellar bodies combine with the cell membrane and release their content into the alveolar spaces. Respiratory distress syndrome (RDS) is a fatal disease that primarily occurs in premature infants, and is mainly caused by the absence or dysfunction of pulmonary surfactant. The alveoli collapse due to surfactant insufficiency impairs the gas exchange in RDS causing respiratory failure. One of the treatment options for RDS in preterm infants is surfactant replacement therapy (SRT), where exogenous surfactant preparations are given to replete the levels of surfactant in the lungs. Prophylactic corticosteroids given at about 24 to 34 weeks of gestation to the pregnant mother may prevent surfactant deficiency in babies as it hastens surfactant production. In this review, we have explored the role of surfactants in the normal functioning of the lungs and different disease conditions.

Keywords: pulmonary surfactant, respiratory distress syndrome, surface tension

INTRODUCTION

Pulmonary surfactant is a complex mixture of lipids and proteins that plays an important role in the normal functioning of the respiratory system. It is a highly surface-active material produced by type II alveolar cells which line the alveoli of the lungs. The surfactant coating the surface of the alveoli reduces surface tension, preventing alveolar collapse, especially during exhalation. Beyond the mechanical function, surfactant's innate defenses shield the lower lobes of the lungs against inflammation and microbial infections [1]. As the first line of host defense, it traps inhaled particles and pathogens, limiting harm while regulating inflammation. It functions both as a lubricant for breathing and a safeguard against pathogens. Through variations in molecular structure across its mixture, pulmonary surfactant maintains airflow in the respiratory system while taking care of all possible damages and microbial incursion into distal airways [2].

Principle of alveolar surface tension

In a water molecule, the oxygen is more electronegative compared to hydrogen atoms. This creates polarity with one side being negatively charged while the other side is positively charged. The opposite-charged sides from different molecules of water are attracted to each other. The bonds thus generated produce the surface tension. Thus, the surface tension can be defined as a cohesive molecular force of liquid created by the attractive forces of the surface molecules which occurs whenever there is an air-water interface [3].

The inter-alveolar septum, the primary site of gas exchange, is the wall shared by the neighboring alveoli. It separates the alveolar space from the capillary lumen [4-6]. Inside the inter-alveolar septum, there are two continuous cell layers; epithelium facing the alveolar lumen and endothelium facing the capillary lumen which forms the barrier that separates air and blood [7]. Due to the presence of an air-liquid interface, surface tension pulls the water as well as the alveoli inwards. The surfactant forms a monolayer at the alveolar liquid-air interface and lowers the liquid-air surface tension of about 70 mN/m to nearly zero on expiration hence preventing alveoli from collapsing [8].

Law of Laplace

Lung recoil is the force that resists lung inflation. The major factor affecting the lung recoil is surface tension. The law of Laplace states that the pressure difference between the air space and the lining (ΔP) depends on the surface tension (T) and the radius of the alveoli ($\Delta P=2T/r$). This pressure attempts to push the air out of the alveoli and hence make them collapse. If surface tension remains the same, this collapsing pressure will increase during expiration when the radius becomes smaller. This is prevented by a change in surface tension throughout the respiratory cycle. When the alveoli expand during inspiration, the concentration of surfactant decreases and the surface tension increases. The opposite is true for expiration when the surface tension is reduced to near zero. This guarantees that the alveoli do not collapse especially during expiration. The absence of surfactant would mean that alveoli would collapse causing poor exchange of oxygen from alveoli to blood and increased respiratory work. Surfactant reduces surface tension to keep alveoli open for gas exchange which reduces the work of breathing. This

emphasizes the critical role of surfactants in lung physiology [2].

A drop of water falling through the air tends to form into a sphere because this shape has the smallest surface area and thus the most reduced energy. Put differently, when the drop is spherical, no additional water molecules can leave the surface. In the switch situation, a round discuss bubble encompassed by water, unbalanced powers acting on surface water atoms cause them to dive into the bulk, which diminishes the surface range and creates pressure within the plane of the air-water interface. This surface pressure acts like a belt fixing around one's midriff. It tends to diminish the volume of the compressible gas interior of the bubble and increments its weight. At equilibrium, the tendency of increased pressure to expand the gas bubble balances the tendency of surface tension to collapse it, which is explained by Laplace Law (Figure A).

The application of Laplace's law is more relevant to the sphere and its role in the mechanics of airway collapse is a topic of argument. Alveoli are not spherical but polygonal in shape meaning their walls are flat, and Laplace's law applies only to a small region where these walls meet [9].

Source of surfactants

Type I pneumocytes which are primarily involved in gas exchange, occupy about 70% of the alveolar surface. They are simple squamous cells and share their basement membrane with the capillary membrane, forming the air-blood interface. Type II pneumocytes occupy about 7% of the alveolar surface. They are smaller in size and secrete surfactant. They can also differentiate into type I pneumocytes (progenitor cells) [10]. These cells also have a role in innate immunity and in transporting sodium and fluid from the apical surface into the interstitium [11]. Alveolar epithelial type II cells produce and organize this surfactant into lamellar bodies, the intracellular storage form of surfactant. Additionally, type II cells recycle the majority of the extracellular

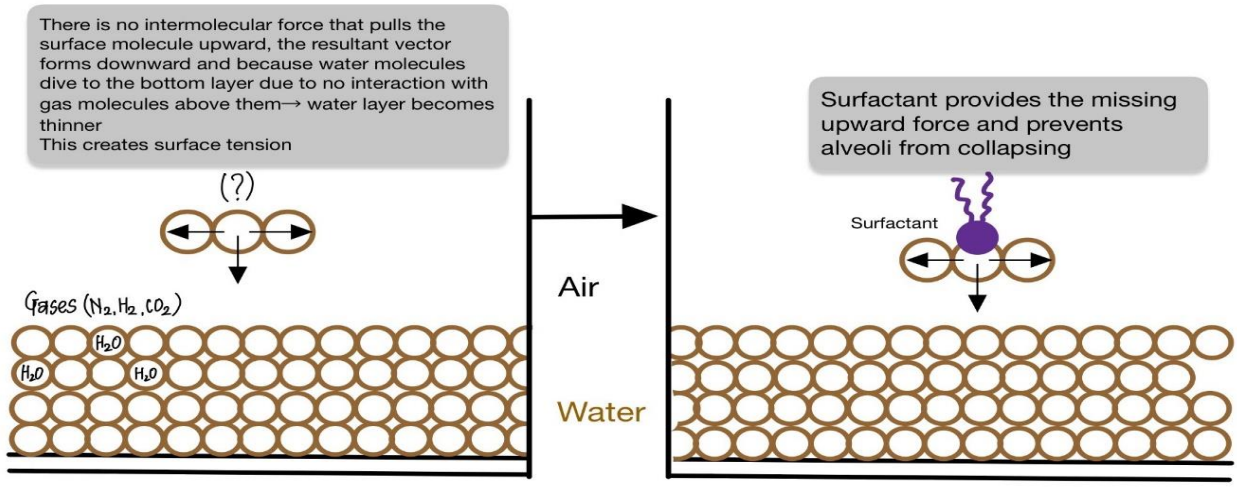

Figure A: Effect of Surfactant

surfactant. Although the surfactant is majorly produced by type II alveolar cells in the lungs, some of the surfactant-specific proteins are synthesized in Clara cells. The synthesis of surfactant starts as shortly as type II alveolar cells start to differentiate i.e. at about 24 to 34 weeks of gestation in humans.

Composition of surfactants

Surfactant consists of a complex mixture of lipids and proteins with additional carbohydrate components. Lipids constitute about 80-90% of surfactants, where phospholipids (90%) are the major component and the remaining 10% is the cholesterol component. Proteins constitute about 5-10% of surfactants [12]. A schematic flowchart of the composition of the surfactant is given in Figure B. The data included is approximate since different review articles had distinct figures.

The phospholipid coats the boundary areas and surfaces from its hydrophobic and hydrophilic properties which is essential for maintaining air-liquid interface [13,14]. The Dipalmitoyl phosphatidylcholine (DPCC) component is responsible for the reduction of alveolar surface tension. It is generated de novo from blood-derived phospholipid precursors and can most likely be converted from unsaturated or recycled phosphatidylcholine. It is divided into two components, Dipalmitoyl (A 16-carbon molecule) which is hydrophobic and is associated with the air component whereas phosphatidylcholine is hydrophilic and is associated with alveolar liquid [15,16]. During intrauterine life, phosphatidylglycerol can be used as a marker of pulmonary maturity which is detectable only in late pregnancy [17]. Other components of surfactant include apoproteins i.e. four surfactant specific proteins (SP) named SP-A, SP-B, SP-C, and SP-D [18].

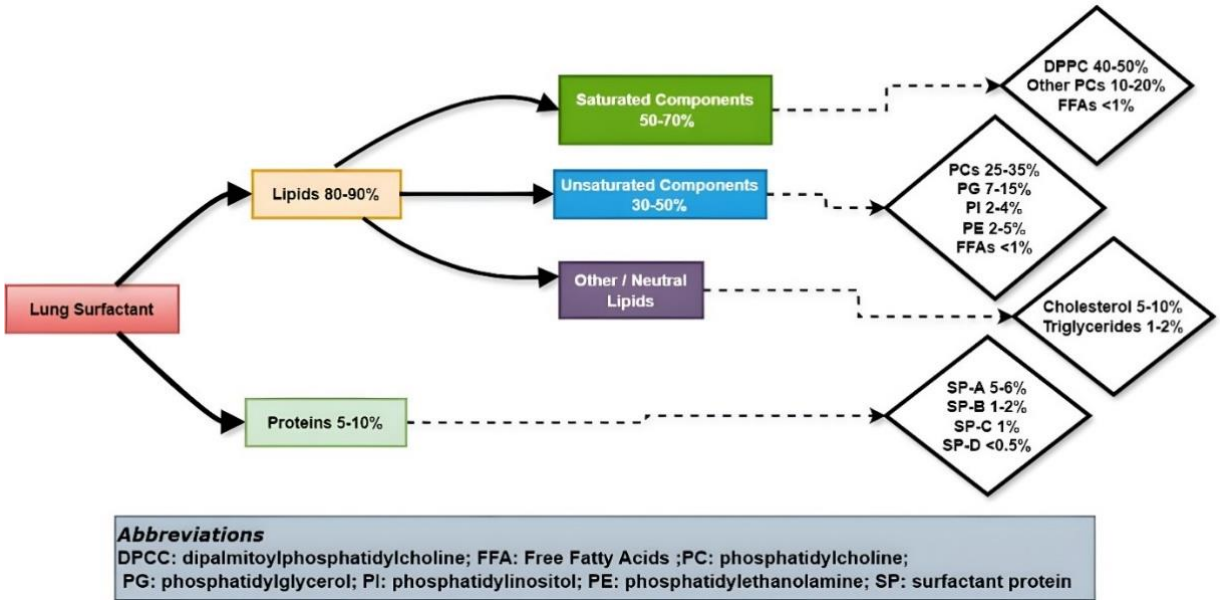

Figure B: Composition and Constituents of Surfactant

Biosynthesis and Metabolism of surfactants

In early life, many transcription factors and other enzymes involved in surfactant lipid synthesis are themselves turned on and activated well in advance of birth. These include lysophosphatidylcholine acyltransferase, choline kinase, phosphocholine cytidylyl transferase, acetyl–CoA synthase, fatty acid synthase, and others. An analogous transcriptional network also controls the formation and exocytosis of the surfactant proteins. The crucial transcription factor for surfactant proteins and lipids is TTF-1. TTF-1 turns on the transcriptional factors that control the expression of surfactant proteins (SP-A, SP-B, SP-C, and SP-D encoded by genes like TTF-1, SFTPB, SFTPC, and SFTPD) and of the surfactant lipid transporter (ABCA3) [18,19]. SP-B is initially synthesized as a soluble proprotein, but several steps in the distal secretory pathway, downstream of the Golgi apparatus, including processing to a smaller lipid-associated peptide, mostly occur in the multivesicular body (MVB) and the lamellar body (LB). These organelles are post-Golgi and intermediate in morphology compared with the Golgi cisternae and the secretory vesicles or granules, called lamellar bodies. SP-B is processed in the LB and MVB by enzymes including napsin A, cathepsin H, pepsinogen C, and likely other enzymes that have not been identified. It promotes membrane-to-membrane contact, modifying lipid packing and facilitating membrane fusion. SP-B deficiency due to known mutations in the gene that encodes this protein in humans (named SFTPB) causes lamellar bodies that are vesiculated in morphology and lack normal bilayer which indirectly hinders the production of SP-C. Properly localized SP-B also seems rare in patients with severe chronic lung diseases and in patients requiring high levels of oxygen to survive. Severe SP-B deficiency (75% reduction of SP-B content in airspaces) is lethal and can cause fatal forms of RDS. Faulty expression of SP-B is consistent with disease pathogenesis in acute as well as chronic lung diseases. SP-C is synthesized in the same way as proprotein which is then transported to the multivesicular body and then to the immature lamellar body. The synthesis of DPPC involves various pathways, including the de novo and remodeling pathways, with enzymes like acyl-CoA: lysophosphatidylcholine acyltransferase (LPCAT1) and choline phosphate cytidylyltransferase (CCTα) playing key roles [19,20]. Several other tissues have transcriptional controls on surfactant lipid metabolism genes, which are controlled by the same transcription factors that regulate fatty acid metabolism and lipogenesis [21]. De novo lipogenesis may also contribute to the intracellular fatty acid (FA) pool in Type 2 pneumocytes. The Kennedy pathway is the primary pathway for PC synthesis in Type 2 pneumocytes, similar to other eukaryotic cells [22]. DPPC from intracellular sources is transported to the lamellar body by means of ABCA3 and stored there until it is released into the alveoli [23-25]. Impairment of lipid metabolism in pulmonary T2C results in surfactant deficiency leading to lung failure and loss of function in ABCA3 resulting in neonatal respiratory distress syndrome and faulty lamellar body synthesis [26].

There are basically two major pools; intracellular and extracellular surfactant components. The intracellular component consists of lamellar bodies which store all the major surfactant products described below and the extracellular component is secreted

into the alveolar space which is collected easily via bronchial lavage [27,28]. Different components make up the whole surfactant pool. The lamellar bodies that are enclosed in the aqueous hypophase and those at the air-surface interaction constitute the alveolar pool of easily obtainable surfactants. (Figure C). When surface tension changes during the respiratory cycle, these lamellar bodies easily dissolve into the surface layer [29]. It has been believed there is an additional surfactant pool fused with type II cell plasma membrane that is stored inside lamellar bodies but has not yet been released. Alveolar surfactants, once secreted, have a half-life in the alveolar space of 5 to 10 hours. This may be taken up by macrophages and/or resorbed into the lamellar structures of type II pneumocytes. Also, as much as 90 % of the surfactant DPPC is recycled from the alveolar surfaces to be reutilized by the pneumocyte type II. It has been shown that the internalization of SP-A by cells is receptor-mediated and has a clathrin-dependent pathway suggesting that one of the receptors that participates in binding of SP-A causes the process [30]. The other 10% goes to alveolar macrophages, which clears up the rest.

At times when there is exhaustion of type II pneumocytes during inspiration, the contents of these lamellar bodies are released. Lastly, there is the de novo production of surfactant and a steady replenishment pool of non-fused intracellular lamellar bodies. There is the role of alveolar macrophage in the uptake and catabolism of both surfactant lipids and proteins and the process depends upon granulocyte macrophage colony stimulating factor (GM-CSF). Mutations in GM-CSF signaling lead to impairment of macrophage differentiation which ultimately leads to

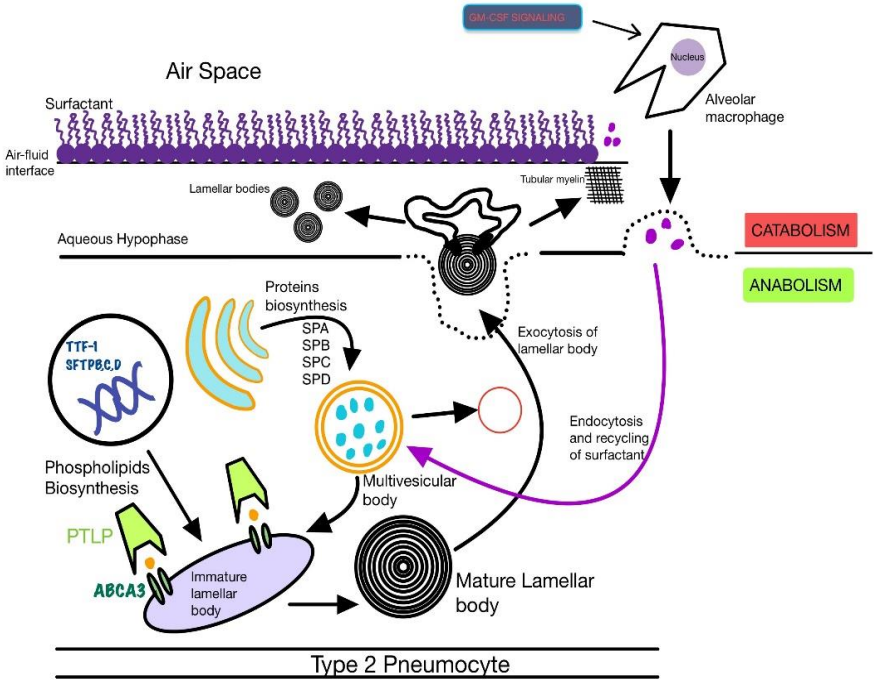

Figure C: Schematic diagram of Synthesis of Surfactant

diminished clearance of surfactant lipids and proteins leading to pulmonary alveolar proteinosis [31].

Biological function of surfactants

The different biological functions are enlisted as below in Table 1.

Table 1: Functions of Lung Surfactant [2,32]

Classification	Function	Description
Biophysical Functions	Lung mechanics	Contributes to lung compliance and reduces work of breathing
	Reduce surface tension	Lowers surface tension at the air-liquid interface, preventing alveolar collapse and atelectasis
	Stabilize alveoli	Maintains alveolar stability during respiration by modulating surface tension
	Prevent pulmonary edema	Counteracts fluid movement into alveoli by creating a surface tension gradient
	Surfactant recycling	Promotes uptake and reutilization of surfactant components
Non-biophysical Functions	Anti-inflammatory	Regulates inflammatory responses in the lung
	Antimicrobial	Provides first-line defense against inhaled pathogens
	Alveolar fluid balance	Influences fluid homeostasis in the alveolar space
	Alveolar macrophage function	Modulates phagocytosis and cytokine production by alveolar macrophages
	Lung development	Crucial for normal lung maturation and alveolarization
	Antioxidant properties	Scavenges reactive oxygen species, protecting alveolar epithelium
	Immunomodulation	Regulates adaptive immune responses in the lung
	Progenitor cell function	Supports survival and function of surfactant-producing cells

Cells involved in pulmonary host defense and pathogenesis

SP-A can be produced by non-ciliated cells in respiratory bronchioles, also known as Clara cells. Its production is regulated by a receptor-mediated mechanism in type 2 pneumocytes [23,33].

The functions of SP-A are listed below [34-36].

- Formation of tubular myelin, which facilitates adsorption of surfactant to the air-liquid interface
- Regulation of phospholipid insertion into the surfactant monolayer
- Modulation of uptake and secretion of phospholipids by type II cells
- Activation of alveolar macrophages for surfactant clearance
- Binding and clearance of bacteria and viruses
- Chemotactic stimulation of alveolar macrophages for pathogen clearance

SP-D has certain structural similarities with SP-A and its function remains questionable. It is thought that its role is mainly in the immunological process [37]. Some studies suggest that it has regulatory function by counteracting the inhibitory effects of SP-A [38]. SP-A and SP-D (together called collectins) control innate immune cells and interact with antigen-presenting cells and T cells (inferring a linkage between innate and adaptive immunity). They play an important role in innate host defense by clearing the

invading microbes. Moreover, SP-A and SP-D opsonize and promote immune cell phagocytosis of pathogens. They inhibit inflammation in acute lung infections, while simultaneously enhancing clearance of pathogens. Yet, this immune cell type is poorly understood in chronic lung disorders including COPD, asthma, and interstitial lung disease. In addition to its immunosuppressive activity, more recent data suggests that the detection of SP-D in serum as well as bronchoalveolar lavage fluid might be developed as a biomarker for some of the non-infectious lung diseases and also in case of traumas. The SP-A and SP-D gene have genetic variants called polymorphisms that can change their structures, functions, and interactions with receptors, potentially impacting disease susceptibility and severity [39]. Both are also proven to play a major role in surfactant hemostasis thereby maintaining surfactant function and metabolism [40].

SP-B aids in phospholipid insertion into the air-liquid interface as well as the formation of tubular myelin. SP-C helps in the stabilization and formation of surfactant monolayer in cooperation with SP-B. SP-B and SP-C (both hydrophobic) proteins helps in maintaining low surface tension in the alveoli by interacting with surfactant lipids and SP-A [34].

Factors affecting pulmonary surfactant

Age: Surfactant levels are lower in preterm infants which leads to respiratory distress syndrome. Their levels also decline with age [41].

Environmental Factors: Cigarette smoke, air pollution, hyperoxia, and ventilator-induced lung injury can impair surfactant function and metabolism from fetal development throughout aging [42,43].

Genetics: The synthesis of pulmonary surfactant is under multifactorial control, regulated by hormones, growth factors, and signalling proteins like SMAD1, with microRNAs like miR-26a playing a role in surfactant synthesis regulation [44]. Mutations in genes encoding surfactant proteins (e.g., SFTPB, SFTPC) can cause surfactant dysfunction and interstitial lung diseases [45].

Oxygen and free Radicals: Oxygen levels and free radicals can regulate pulmonary surfactant protein expression [46], while exposure to high oxygen concentrations can adversely affect surfactant characteristics, leading to reduced pulmonary compliance [47].

Inflammatory mediators: Cytokines, oxidants, and proteases released during inflammation can inhibit surfactant function and promote surfactant inactivation. This also forms the basis of Acute Respiratory Distress Syndrome (ARDS) [48].

Infection: Bacterial and viral infections can disturb surfactant homeostasis through various mechanisms, including direct damage and inflammation [49].

Disease states: Conditions like acute respiratory distress syndrome (ARDS), pneumonia, and pulmonary fibrosis can disrupt surfactant metabolism and impair surfactant function [50].

Disease and Clinical Manifestations

Infant respiratory distress syndrome: Infant respiratory distress syndrome (IRDS)

is primarily caused by the inadequate production or absence of pulmonary surfactant in the lungs of newborns, leading to atelectasis, intrapulmonary shunting, hypoxemia, and hypoventilation [51,52]. The condition can manifest shortly after birth with clinical features of RDS like nasal flaring, cyanosis, grunting, chest retractions and tachypnea [53]. RDS is more prevalent in preterm infants, with a higher incidence in those with lower gestational ages and birth weights [54,55]. Premature infants have qualitative as well as quantitative deficiency of surfactant which predisposes them to Infant respiratory distress syndrome (IRDS). IRDS will develop in nearly half of neonates before 30 weeks of gestation [56]. Occurs in 60-80% of newborns under 26-28 weeks, 15-30% during 32-36 weeks, and seldom in those after 37 weeks gestation [57,58]. Other factors which predispose to IRDS are advanced maternal age, male child, intrauterine asphyxia, and cesarian section [59-61]. The lack of surfactant results in the formation of eosinophilic hyaline membranes and pulmonary atelectasis, contributing to respiratory failure shortly after birth. The pathophysiology involves a disruption of the alveolar epithelial-endothelial barrier, leading to noncardiogenic pulmonary edema and severe hypoxemia.

The diagnosis of infant respiratory distress syndrome (RDS) involves assessing the lecithin-to-sphingomyelin (L/S) ratio, with a ratio less than 2.2 indicating the need for surfactant replacement therapy [62]. Analyzing the L/S ratio in amniotic fluid samples collected via amniocentesis aids in predicting the risk of neonatal RDS, with both gestational age and L/S ratio serving as independent predictors of RDS probability [63].

Surfactant therapy plays a crucial role in the management of respiratory distress syndrome (RDS) in preterm neonates. Studies have shown that surfactant administration in late preterm and term infants with RDS can potentially decrease mortality, air leak, persistent pulmonary hypertension of the newborn (PPHN), and the duration of respiratory support [64]. Early initiation of surfactant replacement therapy (SRT) within the first 3 hours of life is crucial for its effectiveness [65]. Minimally Invasive Surfactant Therapy (MIST) is a promising approach that can help limit barotrauma and prevent lung injury in preterm infants with RDS [12]. Additionally, advancements in monitoring techniques like Electrical Impedance Tomography (EIT) show promise in assessing the distribution and effectiveness of surfactant instillation in the lungs of neonates with RDS [66]. These findings collectively emphasize the importance of surfactant therapy in improving outcomes for neonates with RDS. Monitoring vital signs, providing supplemental oxygen, noninvasive positive pressure ventilation, or endotracheal intubation are crucial for stabilizing the infant's respiratory status [55].

Acute respiratory distress syndrome (ARDS): Acute respiratory distress syndrome (ARDS) is a life-threatening form of severe respiratory failure requiring mechanical ventilation. It is caused by inflammatory lung injury that induces alveolar-capillary leakage and leads to severe hypoxemia with diminished lung compliance. The most common precipitating factor is underlying septic or pneumonic infection that prompts an unwarranted inflammatory reaction in the lung. Any massive inflammation happening in the body is also responsible for the generation of a huge number of chemokines that have an equal possibility to travel the

pulmonary circulation. The released chemokines are responsible for the vasodilation of pulmonary capillaries which ultimately increases the thickness of the alveolar basement membrane creating a hard time for gaseous exchange. Human Neutrophil Elastase (HNE) is one of the main proteases secreted into the alveolar space by infiltrated neutrophils during (ARDS). ARDS presents with acute, diffuse inflammatory lung damage resulting in compromised alveolar-capillary permeability and non-cardiogenic pulmonary edema [67]. This process of inflammatory cascade leads to pulmonary edema and, more strikingly, disruption in gas exchange besides possibly evolving into pulmonary fibrosis [68]. ARDS is not actually due to surfactant deficiency rather conditions precipitating ARDS are responsible for damage of alveolar cells in the long run called Diffuse Alveolar Damage (DAD) and is one of the pathological hallmarks of ARDS [69].

Pulmonary alveolar proteinosis (PAP): PAP is characterized by the accumulation of surfactant-derived lipoproteins within alveolar spaces. It is a rare lung disorder that can cause respiratory impairment and other complications. Pathophysiology involves impairment of surfactant clearance by the alveolar macrophages, leading to alveoli-locking material with periodic acid-Schiff (PAS)-positive proteinaceous accumulation in its lumen [70,71]. This accumulation leads to an impairment in gas exchange and lung compliance that manifests clinically as progressive dyspnea, air hunger, and hypoxemia [71,72], Patients with complications of PAP may suffer from secondary infections (i.e., pneumonia, secondary spontaneous pneumothorax), in addition to cor-pulmonale (right heart failure), leading to right-sided heart failure as a consequence of the increased pulmonary vascular resistance [73].

Other disease conditions include:

Chronic Obstructive Pulmonary Disease (COPD): COPD is a progressive lung disease characterized by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities. Causes of COPD are exposure to noxious particles or gases. The primary risk factor is smoking either cigarette or environmental pollutants, such as biomass fuel and occupational exposures, particularly in low- and middle-income countries [74]. COPD is a collection of two main conditions: chronic bronchitis and emphysema. However, the pathophysiological role of surfactant deficiency in COPD is not very clear [75].

Idiopathic Pulmonary Fibrosis (IPF): IPF is a chronic, progressive, and irreversible interstitial lung disease which is characterized by the formation of fibrosis within the lung interstitium, leading to impaired gaseous exchange and respiratory failure. The cause is idiopathic although various risk factors, such as smoking, environmental exposures, and genetic predisposition have been suggestive of IPF [76]. The disease is characterized by a gradual thickening and stiffening of the lung interstitium, making it difficult for the lungs to exchange gases. Symptoms include progressive dyspnea, dry cough, and fatigue. Several studies have associated IPF with alteration in the composition of surfactants.

High Altitude Pulmonary Edema (HAPE): HAPE is a life-threatening form of non-cardiogenic pulmonary edema that can occur

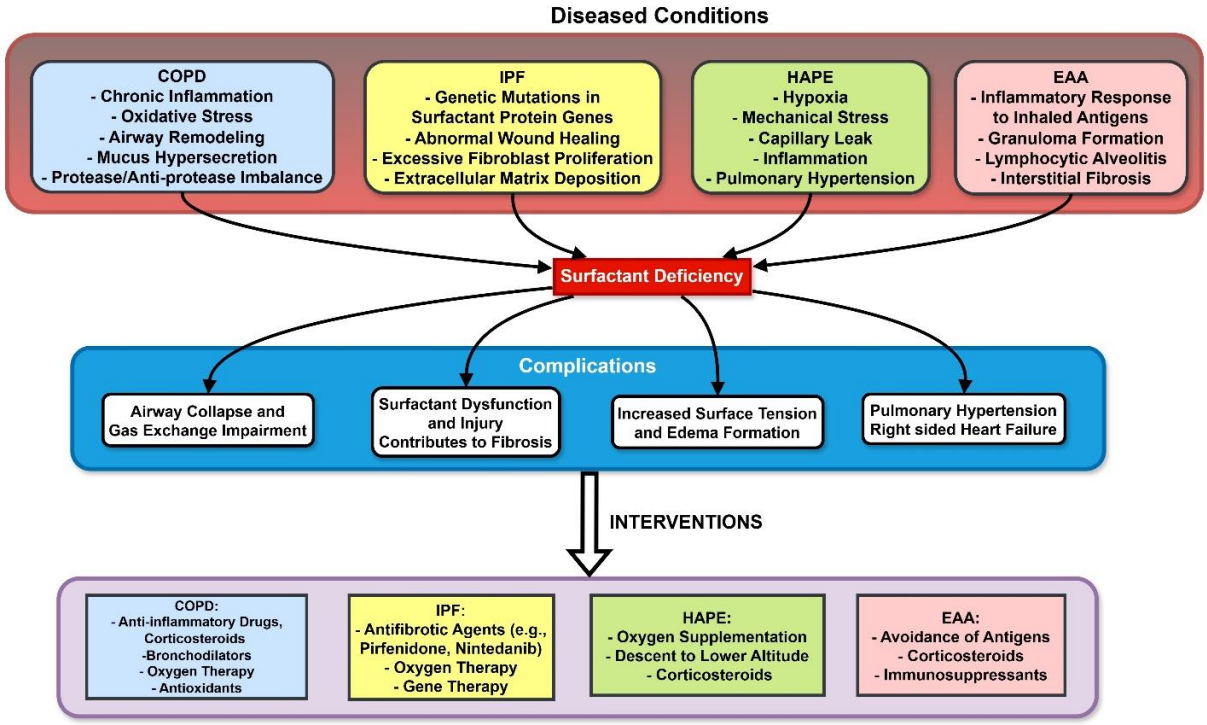

Figure D: Different disease conditions

in individuals who ascend rapidly to high altitudes typically above 3000 meters [77]. It is characterized by the accumulation of fluid in the lungs, leading to impaired gas exchange. Symptoms include dyspnea, cough, fatigue, and, in severe cases, respiratory failure. Prompt descent to lower altitudes and supplemental oxygen are crucial for treatment. Prevention involves gradual acclimatization and prophylactic medication in susceptible individuals. Exogenous Surfactant therapy for RDS at high altitudes is beneficial however there is not much evidence that surfactant therapy works well for HAPE [78].

Extrinsic Allergic Alveolitis (EAA): EAA also known as Hypersensitivity pneumonitis is a condition whose development is associated with the immune response to antigens that circulate in the air, such as mold spores, animal proteins, or specific chemicals [79]. Inflammatory response takes place in the lung interstitium and alveoli and granulomas form. Some of the signs include coughing, difficulty breathing, fever, fatigue, and many others. This may range from when the exposure is acute and intermittent to chronic and progressive where the antigen has a continuous severe toxic effect on the body. The management of this condition includes the identification of the offending antigen and its avoidance, and in some circumstances with immunosuppressive agents or corticosteroids [80].

All the above-mentioned conditions have final common outcome i.e. there is destruction of alveolar cells lining the lungs. When there is damage to type 2 pneumocytes the production of surfactant is hindered and subsequently there is development of increased surface tension in the alveoli and it collapses. Similarly, the destruction of type 1 pneumocytes results in impaired gaseous

exchange and respiratory symptoms. A summary of the diseases is as shown in the Figure D.

CONCLUSION

The role of pulmonary surfactant in reducing the surface tension at the air-liquid interface of the alveolar lining and hence preventing alveolar collapse is well established. The phospholipid component dipalmitoyl phosphatidylcholine along with hydrophobic proteins, SP-B and SP-C are attributed to surface tension–lowering properties whereas more hydrophilic surfactant components, SP-A and SP-D, participate in pulmonary host defense and immune responses. The most significant and well-studied clinical implication is the deficiency of pulmonary surfactant in preterm infants leading to IRDS. Surfactant replacement therapy has become one of the most significant advances in neonatology resulting in a significant decrease in mortality of preterm infants. However, the deficiency of surfactant or its components or the alteration of its composition in several other clinical conditions needs further investigation. Similarly, the role of exogenous surfactant treatment in other respiratory diseases of full-term infants and older children needs to be explored.

Conflict of interest: None declared

Funding: None

Author's Contribution: Concept, design, understanding and review of the literature, and writing the text- **SP, OPY;** Diagrams, reviewed literatures and scripting 2nd draft- **HSY;** revision of 2nd draft and final revision with their intellectual critics- **OPY, SP.** Each author provided their final approval for the anticipated publication.

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