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Review Article

Physics of the Lung: Assessing the Role of Pulmonary Surfactants in COVID-19

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Abstract

Type 2 pneumocytes are responsible for the secretion of pulmonary surfactant (PS) - a surface-active material found coating alveolar spaces - that functions as a corrective mechanism present in human lungs [1,2]. Pulmonary surfactant has been delineated to reduce surface tension and prevent the collapse of alveoli during breathing, while also playing a significant role in the lung's defence against bacterial and chemical invasions [3,4]. PS is composed primarily of lipids (90% by weight), of which dipalmitoyl phosphatidylcholine (DPPC) is most effective in lowering surface tension. PS also constitutes 8 - 10% of associated proteins, namely: SP-A, SP-B, SP-C, and SP-D, that prevent alveolar collapse and maintain lung stability [4].

A reduction in the surfactant levels present in the lungs is most directly associated with the pulmonary condition of Acute Respiratory Distress Syndrome (ARDS), which usually causes hypoxemia, severe oxygen deprivation, blood clots, leakage of blood proteins, pulmonary fibrosis, and atelectasis [5,6]. Currently, the outbreak of the coronavirus pandemic has seen a soar in COVID-19 related ARDS (CARDS), with over 35% of hospitalized COVID patients developing symptoms consistent with ARDS. Upon progression, CARDS increases vascular permeability and deactivates surfactants, rendering the lungs exponentially unstable [6]. CARDS places the lungs at a stage far worse than ARDS from other causes may, necessitating early detection and comprehensive management [3,7].

In this review article, we have explored the physics of the lungs, focusing on the role of surfactants in reducing alveolar surface tension, and how this could relate to COVID-19 [8]. Investigating the feasibility of various surfactant treatments and their role in COVID-19 thus becomes essential for exploration..

Keywords: *Pulmonary Surfactant; Surface Tension; Alveoli; Acute Respiratory Distress Syndrome; COVID-19; Hypoxemia*

Introduction

Covid-19 related ARDS (CARDS)

The novel coronavirus, initially detected in December 2019 in Wuhan, has, since its onset, affected over 150 million people across the world. Declared as a global pandemic, the virus induces numerous symptoms in patients, including fever, pneumonia, respiratory failure and permanent lung damage [9]. A significant number of Covid-19 patients, especially those in critical conditions, further develop symptoms consistent with Acute Respiratory Distress Syndrome (ARDS), which is a lung condition as classified by the Berlin Criteria [10]. The development of this condition in Covid-19 patients is then referred to as Covid-19 related ARDS or CARDS and has been growing increasingly relevant since the spread of the pandemic [10,11].

Covid-19 typically has an affinity for the angiotensin-converting enzyme receptor 2 (ACE2), which plays an important role in controlling blood pressures, and is densely located on the apical surface of the airway epithelia and renal and cardiovascular tissues [12]. Thus, as

they enter through the respiratory tract, viruses carrying Covid-19 tend to destroy cells which predominantly express ACE2 receptors on their surfaces. These include type 2 alveolar cells, or the 'alveoli defenders', which are specifically useful for their production of lung surfactant. Damage to type 2 alveolar cells markedly inhibits the production of lung surfactant, which is required for effective gas exchange, thus causing increased surface tension, alveolar flooding, and atelectasis [12,13]. As the process progresses the dynamic compliance of the lungs are significantly reduced, placing CARDS patients with the immense risk of prolonged mechanical ventilation and alveolar injury [14].

In fact, it has been observed that CARDS patients exhibit a condition of severe hypoxemia [8]. The failure of the hypoxic pulmonary vasoconstriction observed in Covid-19 coupled with alveolar collapse due to a loss of surfactants from ARDS, results in a dramatic increase of intrapulmonary shunting, and subsequently leads to low oxygen levels in the bloodstream [15]. To date, despite various trials and medication regimens, no singular treatment has emerged as highly efficacious in the treatment of patients with respiratory failure caused by CARDS. However, one treatment does show signs of promise- that of surfactant replacement therapy [16].

Pulmonary surfactants

Lung surfactants are considered to be the ideal physiological barrier to viral infections. The lipid and phospholipid layers of their composition play an important role in antiviral activity and the reduction of virus-mediated inflammation and infection [7,8,17]. Moreover, the pulmonary surfactant protein is especially useful in its ability to recognize the Covid-19 spike glycoprotein and subsequent macrophage activation. While the SP-B and SP-C proteins are low molecular weight hydrophobic proteins that are essential for surfactant phospholipid biophysical properties, the SP-A and SP-D proteins are large calcium-dependent collectins which play an important role in the innate immune system [18,19]. Even within a particular cell, surfactants are postulated to interfere with the process of viral replication. The spread of the virus from one cell to another may be interrupted by the presence of a surfactant in the extracellular or interstitial fluid. This effect is most evident at the active site of type 2 alveolar cells and proves beneficial in recognizing and acting upon various invasive infections [8,17].

In addition, surfactants are advantageous in preventing the spread of the coronavirus itself. Considering the most common method of transmission i.e. the droplet contact transmission method, the presence of a surfactant near the cell membrane would interfere with the viral budding process by affecting the viral envelope formation [20]. This would control the contagiousness of the virus and its rate of transmission. Moreover, the manner in which surfactants can inactivate infective viruses is also noteworthy. The possibility of the virus spreading through the bloodstream and other bodily fluids is limited through circulating surfactant molecules with the ability to coat the virus and render it non-infective. Surfactants' ability to lower the surface tension at the air-liquid interface to prevent alveolar collapse, and interact with pathogens to modulate immune responses, renders them extremely relevant in the dealing with the Covid-19 pandemic [21].

Moreover, in order to remain effective, a surfactant must have a number of key properties. Firstly, the rate of its surface adsorption should generate a surface tension of about 25 m/Nm to match the air-fluid interface of the lungs. Secondly, surfactants should be able to prevent alveolar collapse during surface compression and expansion cycles. In order to reduce alveolar collapse, surface tensions must be reduced to nearly 0 m/Nm. Thirdly, during surface expansion, surfactants should reduce surface tension and decrease the pressure difference needed to maintain ventilatory cycles throughout life [5,7,22]. Since the surfactant serves as the interfacial film formed at the air-water interface to reduce surface tension and stabilize the pulmonary system, its depletion brought about by Covid-19 ARDS produces severe lung pathologies and conditions [7]. The severity of Covid-19 related ARDS has prompted several considerations supporting the use of exogenous surfactant in these patients. It is postulated that the administration of surfactant early during the development of respiratory failure coupled with the utilization of a highly functional exogenous surfactant preparation, will greatly favour the potential of this strategy in treating CARDS patients [3].

Exogenous surfactant therapy

The use of exogenous surfactants as a therapeutic option for alveolar collapse and respiratory distress disorders has been most successful when treating premature infants with Neonatal Respiratory Distress Syndrome (NRDS). Currently, clinical data has shown a strong rationale for using exogenous surfactant therapies for CARDS patients as well [23]. According to data published by an article in the Taylor and Francis Journal, 5 out of 5 critically ill CARDS patients in December 2020 showed drastic improvements in oxygenation and compliance within a few hours of surfactant replacement therapy [24]. A second study published in a paper in the BioMed Central Journal confirmed that exogenous surfactant installation via bronchoscopy represents a safe and feasible option in patients with severe Covid-19 ARDS [3]. Exogenous surfactants can prove to be a beneficial mechanism for CARDS patients specifically due to their involvement in the maintenance of lower alveolar surface tension and stabilization of alveolar volume, promotion of gas exchange, reduction of oedema and swelling in alveoli, modulation of systemic inflammatory reactions and reduction of local mechanical forces [19]. However, several unsuccessful attempts of exogenous therapy on ARDS patients in the past have led to increased attention towards the different exogenous surfactant preparations available, the dose and dosing schedule, the delivery method and timing for the initiation of surfactant administration, and the understanding required to optimize and strategize the process further [23].

The primary requirement for the preparation of an exogenous surfactant is the formation of a surface film containing DPPC that is capable of reducing surface tension [25]. Additionally, the consideration of an appropriate dose must also be made, since both concentration and volume amounts will contribute to an overall effect on the patient. The amount of exogenous surfactant being delivered to the lung should be higher than the endogenous amounts typically present, in order to allow for an adequate distribution, and a means of overcoming oedema and respiratory distress. The volume required to deliver the appropriate dose of surfactant should be balanced in a manner that there is a sufficient distribution of the material throughout the lungs whilst also maintaining an appropriate amount of control over areas of said distribution [23,25,26]. This would involve avoiding challenging an already oedematous lung with additional fluid. While the question of redosing and the number of required secondary doses still has no clear answer, greater experimentation will allow for its optimization in the future [27].

Another important consideration for exogenous surfactant therapy is the method of surfactant delivery. Generally, bolus instillation and aerosolization are deemed two common methods when dealing with Covid-19 related ARDS. A third suggested method is that of using a diluted surfactant suspension to rinse over the lungs, thereby removing inflammatory and infectious materials whilst also leaving behind some surfactant contents [3,19]. Bolus instillation is considered safe and feasible as it allows for a large amount of surfactant to be delivered quickly. The technique involves instilling the surfactant suspension directly into the trachea of a patient. Aerosolization on the other hand, allows for continuous surfactant delivery over a prolonged period of time. A further postulation is that aerosolizing agents can be utilized as a means of co-administering drugs such as Ambroxol- an anti-inflammatory and anti-viral substance with the ability to directly impact the release of surfactant from type 2 alveolar cells. A co-aerosolized DPPC-Ambroxol intervention may bring about the alleviation of inherent inflammatory responses, the attenuation of epithelial cell damage, the decrease of interstitial oedema, and hence the reduction of lung damage [3,7]. When co-administered, ambroxol can act as a mechanism for reducing inflammation and minimizing pulmonary capillary permeability, while the exogenous surfactant delivered can act as a means of replenishing the lost substance. In this manner, the spreading of surfactants through the lungs can promote the delivery of Covid-19 related therapeutics and drugs working towards further improving patient outcomes [28,29]. Co-aerosolized substances, then, make up a novel and effective approach of dealing with Covid-19 related ARDS, allowing for both repletion of surfactant and alleviation of pulmonary abnormalities [7].

Currently, the transition towards natural exogenous surfactants has also been on a steep incline. While surfactants can be divided into both organic i.e. natural, and synthetic preparations, the composition of natural surfactants is closest to the endogenous surfactant composition [30]. Natural surfactants include organic solvent extracts of lavaged lung surfactant from animals, or organic solvent extracts of processed animal lung tissue with or without synthetic additives. Synthetic surfactants are preparations that do not include surfactant

material from animal lungs [31]. However, they have proven to be challenging to bioengineer with high equivalence to their endogenous counterparts, and may have side-effects or prove to be costly. Nevertheless, both exogenous surfactant types can be described as feasible in dealing with CARDS patients. Exogenous surfactant therapy certainly forms a substantial potential support therapy for the treatment and progress of thousands of people suffering from prolonged mechanical ventilation. It further forms an ideal treatment option for any and all patients facing critical lung conditions consistent with Covid-19 related ARDS.

Discussion and Conclusion

In conclusion, the role of pulmonary surfactants in Covid-19 is indisputably significant, and an assessment of surfactant levels must form part of the evaluation of Covid-19 patients. The virus will continue to be a health hazard for the foreseeable future, and its effects on reducing surfactant levels that bring about subsequent respiratory failure and permanent lung damage are certainly evident. Moreover, the numerous complexities the virus gives rise to, including that of the pulmonary condition of Covid-19 related ARDS, creates a strong rationale for pursuing exogenous surfactant therapies and treatments. The indication that exogenous surfactant therapy is suited to mitigate the development or progression of pulmonary injury and further form a feasible means of maintaining lung function has been appropriately described. However, understanding the significance of controlling various aspects of the treatment under specifically curated conditions is also imperative in ensuring successful therapy. It is noteworthy that delayed exogenous surfactant therapy can result in epithelial damage, serum permeability, and a high probability of a rejection of the administered exogenous surfactant. Early treatment is, therefore, ideal. Focused efforts towards early identification and management of CARDS can allow for the initiation of treatment in the primary stages of lung dysfunction. Further investigation into the physical dynamics of the airway could yield interesting and novel therapeutic targets for CARDS.

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