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Covid-19, Type II Alveolar Cells and Surfactant

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ABSTRACT

In the case of a Covid-19 lung infection, the virus infects type II alveolar cells which consequently reduce the production of pulmonary surfactant. The surfactant has the function of reducing the surface tension of the alveoli. The less pulmonary surfactant there is, the more the alveoli tend to collapse due to the increased surface tension of their surface. Consequently, the lung would tend to collapse, that is, to reduce its own volume, but collapse is prevented by the muscular movement of inspiration, which instead increases its volume. This means that a "low-pressure area" is created in the interstitial space which attracts liquid and substances which are often inflammatory and which organize over time, giving rise to interstitial pneumonia. I propose to administer the pulmonary surfactant to the patient Covid-19 during assisted ventilation. This technique is routinely used in preterm infants suffering from lack of pulmonary surfactant production due to the immaturity of type II alveolar cells, pending that once matured these cells produce it autonomously. Similarly, the administration of surfactant during Covid-19 lung infection would allow the correct amount of surfactant to be maintained during the acute phase of the infection and would give time for type II alveolar cells to heal and independently resume surfactant production.

Keywords

Coronavirus, Covid-19, Surfactant, Lung, Interstitial Pneumonia, Type II Alveolar Cells, Assisted Ventilation, Pulmonary Ventilator, C-PAP, Easy Covid-19, Pulmonary Interstitium, Pulmonary Alveolus, Type I Alveolar Cells, Surface Tension, Chloroquinine, Azithromycin, Tocilizumab.

Coronavirus infection, Covid-19, becomes problematic for the respiratory system if the infection arrives in the lung. Covid-19 has a tropism for epithelial cells and, in order to replicate itself in the lung, it infects the alveolar II cells of the alveolar epithelium, which are able to replicate thus allowing the virus to replicate.

The alveolar epithelium [1] is composed of type I alveolar cells (squamous cells) [2,3], type II alveolar cells [4,5] and macrophages. Squamous cells are very thin and consequently, although less numerous than type II cells, they occupy most of the surface of the alveolus, about 95%. Squamous cells are responsible for respiratory exchange and are unable to replicate. Type II alveolar cells are able to replicate, giving rise to both type II alveolar cells and type I squamous alveolar cells.

Type II cells contain secretory granular organelles, called lamellar bodies, fused with the cell membranes. These organelles produce pulmonary surfactant [6,7] and secrete it into the alveolar space.

The word surfactant is an acronym for the phrase: surf(ace) act(ive) a(ge)nt and means "superficially active agent". Pulmonary surfactant is a mixture of lipids and proteins. The main function of the surfactant in the alveolus is to reduce the surface tension between the air and the wet surface of the alveolus itself.

The surface tension [8] is the mechanical tension of cohesion of the particles of a liquid on its external surface in contact with a different matter, such as air. The surface tension, for example, allows mosquitoes to walk on the surface of the water, allows a small coin to stay without sinking on the surface of the water placed in a glass (a game we all played as children), allows a glass of to be filled so much that the water does like a small dome above its edge without overflowing. The surface tension causes a drop of liquid in the air, for example water, to have the smallest external surface in relation to its mass.

Surfactants are substances that have the property of lowering the surface tension, for example between a liquid and the air, allowing contact between the two. Covid-19 by infecting type II alveolar

cells heavily interferes with surfactant production.

If only the surface tension acted on the pulmonary alveolus, not opposed by the surfactant, the alveolus would gradually collapse, because the surface tension would tend to maintain the minimum alveolar external surface in contact with the air (as happens to a drop of water which has the smallest external surface in relation to its mass). So, the smaller alveoli would tend to collapse and disappear gradually and consequently the whole lung would tend to collapse.

This tension of the lung to collapse, countered by the inspiratory movement that tries to expand the lung, causes a decrease in pressure in the interstitial spaces. The patient carries out a desperate attempt (using all the inspiratory muscles including the diaphragm) to fill, with air, a lung that tends to collapse, due to the surface tension of the alveoli. This attempt to inhale acts on the lung interstitium like a suction pump. These interstitial spaces start to fill with liquid and anything else that arrives from the blood circuit and which over time tends to gradually develop into interstitial pneumonia.

Summarizing, a Covid-19 infection infects the type II alveolar cells and consequently interferes with the production of the surfactant. Little by little, due to the lack of surfactant with the increase of the surface tension, the alveoli tend to collapse reducing their volume. As a result the whole lung tends to collapse and would tend to decrease its volume. But decreasing lung volume is not possible because inspiratory movement is expanding lung volume. The alveolar volume is reduced due to a lack of surfactant while the lung is dilating in the inspiratory act, so a decrease in pressure is created in the interstitial space. This decrease in pressure tends to attract, in the interstitial space, liquids and substances that gradually organize themselves, giving rise to interstitial pneumonia.

Covid-19 having a tropism for epithelia, including vascular ones, would have a very similar trend to that of some autoimmune diseases, with the production of similar toxic substances. Hence the advantage that there would be in the administration of tocilizumab, also known as atlizumab, a humanized monoclonal antibody used mainly in the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis.

Pulmonary interstitium during inspiration is in a situation that a meteorologist would define as a "low-pressure area". This situation is particularly dangerous because it would attract not only liquid but also these inflammatory substances that would stuff the lung interstitium more and more. This evolution leading to interstitial pneumonia can be worsened by concomitant pathologies that in the inspiratory phase make the entry of air into the respiratory tract more difficult [9].

Severe interstitial pneumonia, with an unmistakable radiographic image, is a late symptom of Covid-19 and the patient in these conditions is usually intubated, connected to a ventilator and is hospitalized in a Covid-19 intensive care unit.

Assisted ventilation is therapeutically motivated at the first symptoms of dyspnea. In less severe cases, non-invasive methods can be used, such as the C-Pap (Continuous Positive Airway Pressure) [10] helmets, which maintain an increased continuous pressure of oxygen-enriched air. Very promising is the idea of Dr. Renato Favero: to transform a snorkeling mask into a device for assisted ventilation with continuous positive pressure [11]. This mask also allows the patient to be positioned prone easily. The prone position is the most suitable position for assisted ventilation for interstitial pneumonia as demonstrated by Prof. Luciano Gattinoni [12].

In severe cases, an invasive method is usually used [13] such as intubating and connecting the patient to the ventilator which actively pumps oxygen-enriched air every inspiratory act. This pressure, exerted in the lung by the air pushed by the pulmonary ventilator during the inspiratory act, prevents small alveoli from collapsing and at best also tends to re-stretch them.

However, even if the patient benefits from assisted ventilation, since the lack of surfactant causes a high surface tension of the alveolar epithelium, in the inspiratory phase there will be a relative "low-pressure area" in the pulmonary interstitium. This relative "low-pressure area" continues to draw into the interstice liquids and substances that have mostly inflammatory characteristics.

For patients intubated using assisted ventilation, I propose to instill the surfactant directly using intubation, precisely to avoid this phenomenon of relative interstitial "low-pressure area". Surfactant can be easily administered to intubated patients as is done in premature babies born with respiratory distress syndrome [14].

After medical evaluation of the risks and benefits, in some cases it may be appropriate, even at the first symptoms of pulmonary dyspnea, to administer surfactants, well before the dyspnea reaches levels that make intubation necessary. Surfactant instillation can be done through a tracheal tube, a technique used in the newborn with respiratory distress syndrome [15]. I propose to try non-invasive techniques of surfactant administration by aerosol in adults with Covid-19 dyspnoic syndrome. Maybe the aerosol route of administration in adults will obtain better results than those obtained (as we read mostly in the literature) in preterm infants with respiratory distress syndrome [16].

Summing up: the administration of surfactant in the intubated patient would avoid the further incoming, in the pulmonary interstitium, of liquid and substances that very often have an inflammatory character. The use of surfactant could prevent the alveoli from collapsing and indeed could perhaps make them re-expand and improve lung gas exchange. Furthermore, the early use of the surfactant would perhaps also limit the need to use intubation.

In preterm infants, where the production of surfactant is not enough, the instillation of surfactant allows the lung to function preserving it as much as possible, waiting for the type II alveolar

cells to mature and independently produce the surfactant. Thus, the instillation of surfactant in the dyspnoic adult because of Covid-19 would allow the lung to function preserving it as much as possible and to pass the time in which there is not enough surfactant (since the type II alveolar cells, which should produce it, are infected). This would allow to better overcome the period of the infectious pathology, waiting for the virus to be won and for new type II alveolar cells to independently produce the necessary surfactant.

Since interstitial pneumonia is the full-blown and extremely severe respiratory manifestation of Covid-19, it makes sense to fight the virus long before it occurs. It is better to let the fever perform its physiological function against the virus, by administering paracetamol only if the fever becomes such as to be dangerous. It is widely believed that the use of antivirals immediately at the very first sign of infection, such as fever and/or cough, is recommendable without waiting for the symptoms to develop into interstitial pneumonia. The use of chloroquine in Covid-19 infection is very interesting, as Didier Raoult and his collaborators have been saying for some time [17]. Chloroquine as an antiviral has already been used, for example against the HIV. It is also interesting azithromycin [18] which is an antibiotic already commonly used in pneumology in pneumonia of uncertain etiology.

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