Biophysical parameters affecting lung surfactant function, surface tension and the transition from aerosol to droplet exhalation (in relation to COVID-19 infection)

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Abstract. A considerable number of biophysical and biochemical studies has increased our understanding of the surface activity of surfactant proteins B and C (SP-B, SP-C) in the (mammalian) lung and their importance for a healthy, proper breathing system. For instance, it is well-known that these surfactant proteins are released from the lamellar bodies of type II cells of the lung alveoli (type II pneumocytes), and that at compression, the lipid-protein monolayer of the surfactant is squeezed into three-dimensional (3D) stacks, acting as a surfactant reservoir. Moreover, studies have demonstrated the influence of hydrophobic nanoparticles on lung surfactant model systems, well before the outbreak of the COVID-19 pandemic. The potentially devastating effect of SARS-CoV-2 infection on vital lung function, including pneumonia and Acute respiratory distress syndrome (ARDS), meanwhile has been confirmed worldwide by thousands of fatal cases, although the mechanism of its onset is not completely understood. In theory, any virus carrying palmitoylated spike proteins (like beta-coronaviruses in general) might interfere with the alveolar surface activity, when infecting the deep respiratory system. However, it is clearly established that SARS-CoV-2 uses the Angiotensin converting enzyme 2 receptor (ACE2) for entry in the host, which receptor is expressed on the same type II pneumocytes, and, as a result, the virus may directly interfere with the secretion of surfactant proteins. This study aims at elucidating the main targets for containment of the spread of the SARS-CoV-2 virus via the respiratory system, a better understanding of the role of virus-surfactant interactions, the formation of aerosols and role of the inflammatory components of the immune system, as well as the role of positive pressure ventilation systems on particle exhalation, as being used at ICUs. Finally, suggestions are made for important goals for future biophysics research in infectious disease prevention and containment.

1. Introduction: Classical and Other Models of Epidemiology

In classical models for the epidemiology of infectious diseases, a deterministic approach is followed, based on the division of the population into Susceptible (S), Infectious (I) and Recovered (R) individuals, called a S-I-R-based epidemic model [1]. According to this S-I-R-based model, founded by Kendall in the nineteen fifties [2], mathematical deduction implies that an epidemic necessarily develops into a pandemic, once a pandemic threshold is exceeded, resulting in the spreading of the infectious

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agent over the global population [3]. In the case of the present COVID-19 pandemic, however, a number of anomalous characteristics urge for a re-consideration of this SIR model, namely with regard to the notions of being 'susceptible', as well as being 'infectious' and having 'recovered' from the disease. For, not only there is a strong correlation between age and case fatality ratio (CFR), there has been a lot of confusion and misleading information too, about the infectivity of the SARS-CoV-2 (COVID-19) at young age of the infected person, about the susceptibility for COVID-19 in youngsters below the age of 18, and most of all, about the possible recovery from the disease and eventually acquired immunity in all age groups [4]. In recent history, alternatives for Kendall's deterministic model for the spread of infectious diseases have been proposed, e.g. in the group of Barabasi [5]. From a humanitarian and public health perspective, however, it would become helpful to develop mathematical tools for modeling the development of disease progression (at an epidemiological scale), i.e. at unraveling the factors that cause the transformation of a mild coronavirus infection into a severe distress of the respiratory system.

2. Biophysics of the Mammalian Lung and Lung Surfactant Function

In order to model the process of respiration at the mammalian lung, it is important to know the biophysical features of a healthy lung function. The mammalian lung is an organ where gaseous exchange takes place between the air in the lung alveoli and the blood in the alveolar capillaries. Due to the fine ramifications of the bronchiole into some 3.10^8 alveoli with an average diameter of 200-500 μm, in adult humans, in optimal conditions a large area of 70 to 100 m^2 is available for gaseous exchange. At normal atmospheric pressure, this results in surface tensions in the range of centi-newton per meter. Due to the fine alveolar structure, the risk of collapsing when pressure drops, or the risk of breaking at higher tensions, is real. Therefore, a liquid mixture of lipids and surfactant proteins (named surfactant A to D) enables the lung alveoli to maintain surface tension when alveoli expand or when pressure drops. The most important molecular component of this surfactant mixture is surfactant protein B (SP-B)(and also to some extent, SP-C), which forms stacks of protein layers at low pressure and that may spread at extension of the lung alveoli (at high internal lung pressure)[6]. The other surfactant proteins A and D are suggested to be functionally related with immunological and host defense mechanisms [7]. Due to the hydrophobic nature of SP-B, chemical interactions with hydrophobic moieties have an important effect on surface behavior and mechanical stability of pulmonary surfactant films [8, 9]. Moreover, hydrophobic polymeric nanoparticles exert size-dependent influences on the domain morphology in lung surfactant models [10].

Already in 1993, it was reported that a human infant died from respiratory failure in the postnatal period, in association with a lack of SP-B protein in airway secretion [11, 12]. Also in SP-B knockout mice, animals die of respiratory failure after birth [13]. Ultrastructural research has shown that synthesis and secretion of SP-B protein (in so-called lamellar bodies) takes place in the type II epithelial cells (pneumocytes) of the alveoli [13](as well as in the Clara bronchiolar epithelial cells) [14]. Unfortunately, the SARS-CoV-2 virus uses the Angiotensin converting enzyme 2 receptor (ACE2) for entry in the host, which receptor is expressed on the same type II pneumocytes [15]. Since the intracytoplasmic coronavirus replication makes use of so-called double-membrane vesicles inside the host, at least in a model system using another member of the *Coronaviridae*, namely the *Mouse Hepatitis Virus* (MHV) [16], it is suggested that virus replication also interferes with lamellar body formation and SP-B secretion from these pneumocytes.

With respect to the healthy, non-infected lung, the interaction between surfactant proteins and other extracts from native surfactants, results in hysteresis-like, quasi-static compression/expansion isotherms

[8], enabling the protection of the alveolar morphology during the (normal) respiratory pressure changes. The mathematical theory of hysteresis, such as occurring in well-known physical phenomena like elasto-plasticity or ferromagnetism, implies the notion of bi-stability and involves the use of complex mathematical notions like hysteresis operators [17]. The stacking of surfactant B protein – possibly together with other components of the surfactant mixture - is probably the key mechanism for a healthy response to compression and dilatation of the alveoli. In case of COVID-19 pneumonia, however, it is obvious that the conditions for normal lung surfactant function are absent, sometimes literally due to the filling of the lungs with blood (hemorrhage) or due to (generalized) pulmonary intravascular thrombosis [18].

3. Anomalous Features of the COVID-19 Pandemic and Acute Lung Injury

Since the discovery of the SARS-coronavirus (CoV-1) in 2002, and the subsequent outbreaks of *Middle East Respiratory Syndrome* (MERS) and the SARS-CoV-2 in 2019 (COVID-19), the world has witnessed a series of coronavirus epidemics and a pandemic resulting in severe lung injuries and high case fatality ratios (CFR)[3, 15]. Following the first CoV-pandemic, it was suggested that the high mortality rates may be immunopathological in nature, meaning that the *Acute Respiratory Distress Syndrome* (ARDS) is in fact due to an overreaction of the immune system [19], also called a cytokine storm. Beside the differences between SARS-CoV-1 and CoV-2, a number of high risk comorbidity factors have already been demonstrated, although many questions remain unresolved with respect to age dependence of the severe adverse reactions of the immune system, age-dependent infectivity and susceptibility to virus infection. These are not standard features included in the classical S-I-R model developed by Kendall and followers [2].

Typical features of COVID-19 that show a strong association with severity of the disease and mortality, appear to be the formation of D-dimer (a fibrin degradation product resulting from blood coagulation) and the presence of so-called ground glass opacities (GGO)(obstructions) in the lungs [20]. With respect to the intensity of virus shedding by an infected and diseased person, statistical evidence became available already during the early phase of the pandemic [21]. On the other hand, modeling the amount of virus shedding (dependent on age, comorbidity factors, inflammatory parameters and development of fever, time between disease onset and hospitalization) and incorporation of these factors in epidemiological modeling of the spread of the disease, as well as for taking the correct protective precautions and regulations, however, appeared a difficult task for the various governments. It seemed as if each country developed its own models, protective measures and regulations. Especially with respect to the beneficial use of prophylactic medication, the possible spread of the virus via (indoor) aerosols and with respect to the acquisition of herd immunity by populations infected at large, a lot of confusion and contradictory information appeared to roam around at social media, but also at officially approved institutional websites.

For a return to a sound scientific approach, it may become helpful to make a methodological distinction between S-I-R-modeling of classical infectious diseases – which would become instructive when an effective vaccine becomes available for large parts of the population - and the epidemiology of immunological dysfunction (like e.g. the rise of allergic diseases)[22]. Also the understanding of a proper functioning of the lung, starting from its biophysical and anatomical characteristics, might shed some light on the severe risks associated with lung injury, regardless the viral source or other contaminating factors (see ⁋ **4. Modeling the Fractal Lung, Surface Tension and Droplet Exhalation**).

4. Modeling the Fractal Lung, Surface Tension and Droplet Exhalation

The organization of the mammalian lung is one of the organs that best corresponds with a fractal organization, in the sense of Mandelbrot [23]. In the adult, healthy lung, a classical, deterministic scaling of the lung architecture is achieved following the formula:

$$S(z) = S(0) \cdot \alpha^{z}$$

where S(0) denotes the respective tracheal dimension and z the generation order of bifurcations of the bronchioles; for $0.67 < \alpha < 0.73$ good approximation with morphometric data is obtained [23].
In general, with a probability function $P(\alpha)$ describing any distribution of scaling functions of the z/α^{th} generation, following Nelson *et al*. [24], the scaling relationship becomes:

$$S(z) = \int_{0}^{\infty} S(z/\alpha) P(\alpha) d\alpha$$

An alternative representation of airway scaling was proposed by West *et al*. [25], resulting in an inverse power-law distribution:

$$S(z) = z^{\mu} \cdot A(z)$$

with μ representing the power-law index (also called fractional dimension), and $A(z)$ a function that reflects harmonic periodicity and that can be used for fitting morphometric data. According to Sturm [23], another modification of the formula above gives the best correspondence with morphometric data, resulting in the following (inverse) power-law description for airway scaling:

$$S(z,n) = z^{\mu} \cdot F(z,n)$$

with $F(z,n)$ a tailor-made function in order to represent the complexity of the mammalian lung: not only it is a generation-related function that allows for optimal fit of morphometric data, it is also adapted for intra-subject variability that follows a chaotic distribution around mean morphometric values [23].

Whatever function is chosen for optimizing the morphometric data, however, it is obvious that this situation only describes the healthy, uninfected lung. From the power-law description for airway scaling, a power-law rating of lung injury (P_{inj}) may be inferred, where θ denotes the generation order of infection:

$$P_{inj}(z,n,\theta) = z^{\theta-\mu} = \frac{z^{\theta} \cdot F(z,n)}{z^{\mu} \cdot F(z,n)}$$

which is simply the proportion of the injured part of the lung compared to the healthy lung. An important result hereof, however, is that also the lung capacity impairment obeys a power-law description. Moreover, with a severely impaired lung capacity, the lung alveoli become less protected by the surfactant mixture against (mechanically induced) air pressure (see ⁋ **2. Biophysics of the Mammalian Lung and Lung Surfactant Function**). As a result, positive pressure mechanical ventilation, when not adapted for the diminished effective lung alveolar surface capacity, may lead into a iatrogenic contribution to disease aggravation; moreover, it may also result in increasing the spread of viral nucleic acids and proteins across damaged endothelial barriers [18].

With regard to the spread of viral particles in closed indoor environments, numerous studies have stressed the importance of a proper ventilation and air filter systems. Less well-known are the biophysical parameters affecting the interaction between virus particles and the liquid mixtures in the respiratory system. Due to the palmitoylation of the virus envelope and spike proteins (in the family of *Coronaviridae*)[26], the virus is expected to be well soluble in hydrophobic liquids, just as the SP-B protein fraction of the lung surfactant mixture (see above). These chemical properties are both

interesting in order to eliminate the virus and to contain its spread, and, it is also important to understand the virus shedding and infectivity, especially in indoor environments.

Public awareness has been raised to deal with the habit of sneezing and coughing in public spaces. It has been suggested that coughing may cause the release of 10^5 droplets at the time, at an average speed of 50 mph (80 km/h), whereas during sneezing even speeds of 100 mph are reached. The science of rheology or fluid dynamics describes the use of dynamic, resp. kinematic viscosity and resulting Reynolds number in order to describe the transition from a steady laminar flow into a brusque, vehement turbulent flow, like produced during sneezing. Specific adaptations of the theory of fluid dynamics have been described for flow transition in physiological circulation systems, for instance making use of the Hagen-Poiseuille's Law of hemodynamics in blood circulation [27]. However, what causes the body to sneeze is a complex interplay between a multitude of factors, also called a semi-autonomous reflex. Not only pathogenic, infectious organisms, airway-irritating substances as well as innocuous environmental antigens [22], but also dysrhythmia of the autonomous nervous system, such as apnoea or gastric hypermotility (due to activity of the X^{th} cranial nerve) and even the photic sneeze reflex (PSR) - an uncontrolled stimulation of the trigeminal nerve (V^{th} cranial nerve) - may also evoke sneezing; the latter is suggested to be part of a trigeminocardiac reflex aberration [28]. So, although sneezing may be part of some harmless manifestations of a hyper-active immune or autonomous nervous system, it is especially injurious (to public health) when it occurs in infected individuals that carry the virus, but that are without other symptoms (like often in the young generations affected by COVID-19). This is another reason for making a sharp distinction between the epidemiology of severe viral infections and the epidemiology of (mildly) affected or disfunctioning immune (and autonomous nervous) systems.

5. Suggestions for further Research

In biophysical research, a lot of knowledge has been gathered regarding the interaction between surfactant proteins, nanoparticles and hydrophobic chemicals in model systems mimicking the healthy lung. The study of interactions between coronavirus proteins and nucleic acids with cells in the normal mammalian lung, remains a target for high risk level biosafety laboratories. Especially the mechanisms that have a crucial impact on virus shedding and infectivity, and the virus characteristics that are important for the development of an effective vaccine, already are prioritized by the pharmaceutical research community.

From the epidemiological viewpoint, also a lot of questions need to be clarified in order to understand the spread and containment of COVID-19, such as the influence of age, gender, medical status and a number of co-morbidity factors. Above all, an alternative for classical, epidemiological S-I-R-modeling is needed in order to understand the unexplained rise in immune-deficiencies in a broad spectrum of the population and how these immune-related disorders may affect the disease progression in virus infections like in COVID-19.

Mathematically, new insights may come forward from the understanding of the influence of factors affecting the fractal lung architecture upon a normal, healthy lung function. ■

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