Lung Damage Mechanisms For COVID-19 and Other Lung Infections, and Driving Force in Leukecyte Recruitment and Migration

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Abstract: To understand lung damage caused by COVID-19, we deduced two-phase lung damage mechanisms. After the lungs are infected with SARS-CoV-2 virus, the affected lung tissue swells and surface properties of pulmonary capillaries change, resulting in an increased flow resistance of affected capillaries. If a sufficient number of capillaries are affected by the infection, the swelling and increased cell wall adhesion collectively raise pulmonary vascular resistance. The increased vascular resistance further increases the dwell times of WBCs in affected capillaries and nearly capillaries. When pulmonary pressure is sufficiently higher, WBCs are forced to squeeze into interstitial spaces or alveolar spaces when local pressures are higher than what the capillaries can withstand. When more and more WBCs are dynamically retained, the flow resistance of more capillaries rises, pulmonary vascular resistance rises, and pulmonary pressure rises. The rise in the pulmonary pressure in turn results in elevated capillary pressures. When capillary pressures around the alveoli are sufficiently high, they cause interstitial pressures to change from normally negative values to positive values. The positive pressures cause fluid leakage to the alveolar space and thus degrade lung function. Tissue swelling, and occupation of WBCs in interstitial spaces and alveolar spaces further reduce compressible volume, and thus cause further rise in the pulmonary vascular resistance and pulmonary pressure. When the pulmonary pressure has reached a critical point as in the second phase, the blood breaks capillary walls and squeezes through interstitial spaces to reach alveolar spaces, resulting in irreversible lung damages. The available free volume in the thorax cage, organ usable capacities, temperature and humid are expected to have great impacts on degree of lung damages. The free volume in the thorax cage, lung usable surplus capacity, and other organ usable capacities determine the arrival time of last-phase irreversible damage. The mechanisms imply that the top priority for protecting lungs is maintaining pulmonary micro-circulation and preserving organ functions in the entire disease course while controlling viral reproduction should be stressed in the earliest time possible. The mechanisms also explain leukecytes are recruited and migrated into inflamed tissues by increasing their dwell times caused by increased local flow resistance.

Keywords: SARS-CoV-2 COVID-19; lung damage mechanisms; leukecyte recruitment; viral infection; immune response; temperature and humidity; interstitial pressure change

INTRODUCTION

The pathological features of lung damages caused by SARS has been described [1]. The lungs were edematous and increased in weight with extensive consolidation. The damages include extensive edema, glossy membrane formation, collapse of alveoli, scaling of alveolar epithelial cells, and fibrous tissue in alveolar spaces. The pathological features of damaged lungs of COVID-19 patients has been

reported [2]. One patient died from a sudden cardiac arrest. The lungs in the patient showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates. The left lung tissue displayed pulmonary oedema with hyaline membrane formation. Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were seen in both lungs. To find best treatments for the COVID-19 disease, it is essential to understand the mechanisms by which the lungs are damaged by COVID-19 virus.

METHOD

In this theoretical study, we used data from published articles on the COVID-19 diseases, lung structure, lung physiology, physiological data, microvascular rheology, and hemodynamics, etc. When lung tissue inflames, the lungs need free volume to accommodate the volume expansion of swelling tissue. Pathological studies show that WBCs are accumulated in the lungs. When WBCs are dynamically retained in the lung tissue, they occupy some of compressible volume in the thorax cage because lungs are highly compressible, deformable, and extensible. The percentage of free volume taken up by WBCs is an important indicator of the lung's ability to accommodate further tissue swelling. We conducted several simulations to see how the net dynamic retention of WBCs at various percents can take up free compressible volume in the thorax cage. Net dynamic retention rate is defined as the difference between the percentage of WBCs that enter the lungs and the percentage of WBCs that exit from the lungs. Retained WBCs are accumulated in the lungs with time, and loss of compressible volume is same as the total volume of all retained WBCs over a period of time.

RESULT

A. Two-Phase Lung Damage Mechanisms

White blood cells ("WBCs") pass through pulmonary capillaries [3, 4]. There is a great size discrepancy between the mean diameter of circulating leukocytes (6-8 μm) and that of the pulmonary capillaries (~5.5 μm) [4]. Small lymphocytes sizes range from 7 to 10 μm in diameter; large lymphocytes sizes range from 12 to 15 μm; and monocyte size ranges from 15 to 30 μm [4, 45]. Reported sizes of WBSs depend on sources, differentiation state, measurement methods, and cells composition, most WBCs must move through pulmonary capillaries by deforming themselves or squeezing through.

1. Inflammation-driven progressive lung damage process

The endothelium actively participates in controlling blood flow, and affect permeability, leukocyte infiltration, and tissue edema [4, 5, 6]. The changes in epithelial cells disrupt blood homeostasis by increasing capillaries vascular resistance. Other changes include flow dysregulation, thrombosis, and capillary leak [5]. The origin and differentiation cues for many tissue macrophages, monocytes, and dendritic cell subsets remain unclear [7]. The knowledge of retention of leukocytes provides several hints. All WBCs are produced and derived from multipotent cells in the bone marrow known as hematopoietic stem cells. As long as leukocyte concentration in blood can be detected at certain level, a considerable part of them must enter the lung tissue and exit from the lung tissue except

those that die. We can deduce that the cell retention time depends on elasticity of the capillaries. Second, the micro-vascular network of capillaries can be blocked by an excessive number of retained of WBCs. Finally, blood viscosity is an important influencing factor, and so are all factors that affect blood viscosity.

Figure 1 shows how the retention of WBCs is responsible for damages to the lungs.

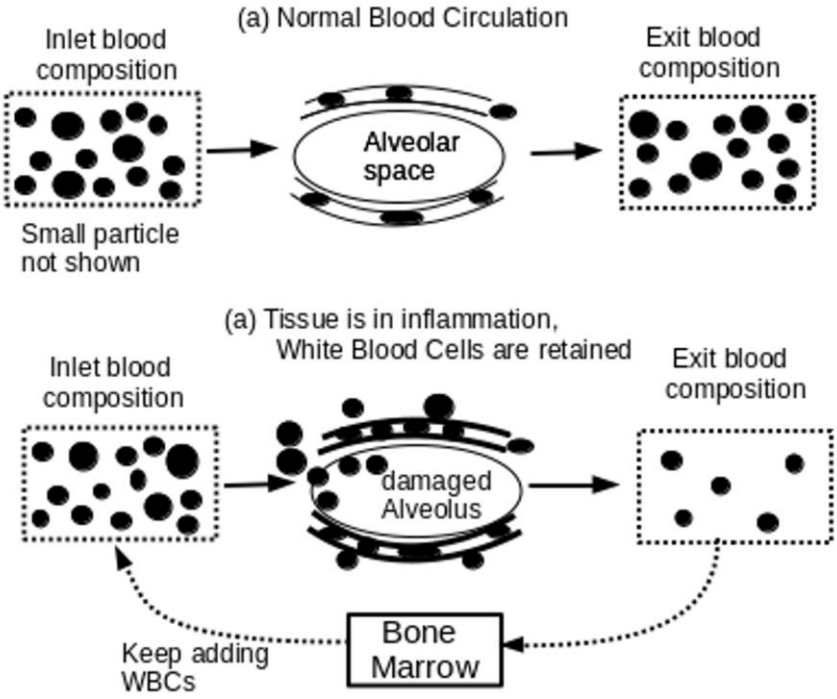

Figure 1, diagram (a) shows how WBCs squeeze through capillary network with much smaller pores. Diagram (b) shows that when the tissue is in inflammation, the walls of capillaries are changed and the occupation of WBCs in the interstitial spaces will generate normal force against the walls of capillaries, and thus raising friction against the moving of WBCs. Some large WBCs, particularly the largest ones, are dynamically retained and thus result in higher capillary pressure. Initially, water leaks out from the capillary and passes through interstitial spaces to reach the space of the alveolus. When local blood pressures rise further to pass the threshold that most capillaries walls can withstand, as in the second phase, the circulating blood force WBCs to break through capillaries walls and squeeze through the spaces between epithelial cells to reach the spaces of the alveoli.

Early phase Infection leads to swelling and changes in epithelial cells, raises vascular resistance of pulmonary capillaries, raises local capillary pressures and increases interstitial pressures. Normal capillary pressure at a middle point is about 7 mm Hg. If the capillary is blocked in the venous side, the pressure is same as the arterial pressure (about 15 mm Hg mean). This results in increase in the interstitial pressure. The reversal of the interstitial pressure leads to fluid leakage to the alveoli, and, if the capillary pressure is too high, the blood raptures epithelium of alveoli and reach alveoli inner spaces in a limited number of alveoli. In the early phase, damages to alveoli take place as sporadic incidences.

Lungs are a highly expandable organ. A healthy adult can have 3000 ml inspiration volume while the normal breathing takes about only 500 ml volume [8]. This implies that lungs have about 2500 ml compressible space, including the space generated by downward moving of the diagram. However, blood is incompressible because both water and all blood cells are incompressible. Thus, the leakage of blood reduces available volume for capillaries to expand, and has an equivalent effect of reducing capillary compressibility or elasticity. Affected tissue has an increased vascular resistance to blood circulation, and thus further promotes retention of WBCs at higher rates.

If the inflammation is of a limited degree, the slower traveling speed of WBCs has an effect of extending the WBCs' dwell times so that they can have more time to contact infected cells and foreign matters. However, on a long term basis, the number of entering WBCs must substantially be equal to the number of exiting WBCs. We refer this requirement as WBCs transport balance for convenience.

The infection disturbs the WBCs normal transport balance. As a result, some WBCs may stay in the capillary for too long while certain large WBCs may be caught indefinitely. The infected tissue keeps retaining WBCs. By accumulative effects, the occupation of WBCs in interstitial spaces and slow-travel of WBCs in capillary pores result in higher vascular resistance. The retention of WBCs results in a reduction of WBC concentration in blood. A reduction of the WBCs concentration in the blood causes bone marrows to generate more WBCs [3]. When newly arrived WBCs travel through the lungs, they are again caught and retained partially and dynamically. Eventually, accumulated WBCs occupy too much of interstitial spaces; and leaked fluid and blood exudates fill more alveolar spaces. The pulmonary vascular resistance reaches the maximum and shuts down pulmonary circulation as heart arrest or multiple organs failure. The most obvious damages are found on alveoli. Alveoli are filled with viscous materials and WBCs [2, 3].

Healthy lungs are highly elastic, deformable, and compressible and have ample volume for accommodating volume changes during breathing cycles. While the WBCs are accumulated in interstitial spaces and alveolar spaces, blood circulation in affected locations becomes worse and worse. In the affected locations, normal blood circulation is increasingly replaced by extremely-slow diffusion process. As a result, some lung cells may die from lack of energy and oxygen. To fill dead tissues, lungs generate fibroblastic cells.

The total volume of compressible alveolar spaces is estimated to be 2000-3000 mL. Since at least part of this compressible space is attributed to reduced lung blood volume, we use 2000 ml. The heart of an adult person pumps blood at 5 liters per min, The pulmonary flow is essentially same as the cardiac output. WBCs make up approximately 1% of the total blood volume. It should be noted that WBCs are dynamically retained by increasing their dwell times or reduce the traveling speeds. Despite the complexity, dynamic retention is equivalent to retention of a certain percent of WBCs in the lungs (even though some slowly travelling WBCs eventually pass through the lungs). We use this simple approach because the fraction of lung volume taken by WBCs is the most important criterion. Assuming that only 0.1% of the WBCs are "retained" for any time increment, the retention rate would be equivalent to 0.05 ml volume of WBCs per minute. The retention of WBCs in interstitial spaces has the same effect of reducing the volume of alveolar spaces because the total volume of the lungs is substantially fixed. In addition, fluid filled in alveolar spaces is not compressible.

Table 1 Percent of Lung's Compressible Volume Filled By Blood Exudate Increases with Time (Based on 0.1% WBCs net retention)

Ret. Vol.(ml/min)	Time (min)	Time (days)	Exudate Vol (ml)	Compressible Vol. (%)
0.05	1	1 min	0.05	0.0025
0.05	60	1 hour	3	0.15
0.05	1440	1 day	72	3.6
0.05	7200	5 days	360	18
0.05	14400	10 days	720	36
0.05	28800	20 days	1440	72
0.05	43200	30 days	2160	Over-limited

Lung compressible volume=2000 ml, blood flow rate=5 liter/min, WBC=1% of blood volume and WBCs retention rate=0.1%.

The filled volume can also be estimated by computing the WBC volume. In a normal adult, there are 4.3-10.8 × 10(9) WBCs per liter of blood. Assuming 0.1% of the largest WBCs are retained in any given time, we got a similar trend.

2. Critical point of irreversible lung damages

We found there is a critical point for the lungs to experience irreversible damage. The systolic pulmonary pressure is about 25 mm Hg and diastolic pulmonary pressure is about 8 mm Hg, with the mean pulmonary arterial pressure being about 15 mm Hg. The negative pressures (about -1 to -3 mm Hg) in interstitial spaces is maintained by the flow caused by lymphatic pumping, and net osmotic pressure. Extra fluid that has been on alveoli is sucked back to the lung interstitium through the small openings between epithelial cells. Damage to the capillary membrane causes leakage of fluid and plasma proteins and thus result in an increase in the interstitial pressure. The edema of the interstitium results in a rise in interstitial pressure, which can cause immediate rapture of the epithelium.

When a sufficient number of capillaries are "blocked" by slow-moving or retained WBCs, the overall vascular resistance rises; and slow-moving WBCs in capillaries reduce the compressible volume of the blood vessels in the lungs. An elevated pulmonary pressure in turn raises capillary pressures surrounding all alveoli. The interstitial pressures are directly related to capillary pressures, and become positive when venous pressure is elevated [8, 9]. If the capillary pressure around an alveolus is raised to sufficiently high, it overcomes the negative interstitial fluid pressure. There must be a point at which the pressure at the interstitial space is changed from the normal negative value to a positive value. It is inferred that after a sufficient number of WBCs has been retained, the elevated pulmonary pressure has a global impact on the lungs: the lost negativity of the interstitial space loses the protection against moisture damage to alveoli, and the elevated capillary pressure forces blood to break a large number of pulmonary capillaries. For this reason, infection of a sufficient number of alveoli can cause damage to substantially all alveoli through raising the pulmonary pressure.

3. Potentially doubly exponential damaging curve

In the above computations, we did not consider two self-aggravating factors. We predicted that lung function degrades potentially by a doubly exponential curve for the following reasons. First, retained WBCs and lung swelling are expected to make pulmonary vascular circulation progressively worse. The resultant failure to maintain energy metabolism further aggravates inflammation and

diminishes the heart ability to maintain required pulmonary vascular circulation. Thus, the speed of lung damage at a later time is faster than that at previous time intervals. Moreover, the lungs have a fixed total volume and certain expandable volume required for normal breathing. The effects of retaining WBCs on pulmonary vascular resistance cannot be linear.

When the compressible volume inside the thorax cage has been substantially replaced by fluid and retained WBCs, the pulmonary vascular resistance will rapidly rise with further retention of WBCs. This results in retaining substantially all WBCs and rapidly raises pulmonary pressure. The elevated pulmonary pressure forces blood to squeeze into and through any spaces in the entire lungs. It may take a short time, possibly in a matter of less than an hour to complete the final stage of irreversible damages. When substantially all compressible or deformable spaces are occupied by WBCs and fluid, the pulmonary vascular resistance approaches the maximum, pulmonary flow reaches zero, and lung function approaches zero. There is no way to reverse.

Considering the potentially doubly exponential damaging process, we estimate that dynamic retention rates of WBCs could be 0.01%-0.1% initially, increase to 0.1% to 1% when the lungs lose most function; the blood rapidly fills the voids in the lungs finally. Our ballpark prediction is consistent with the rapid disease course from shortness of breath to death [3]. The damaging process implies that the problem is correctable by using right methods only in the earliest time. We cannot overstress the importance of this strategy.

4. Physiological injury of low temperature to the lungs

A low temperature causes capillaries to contract to add more friction to WBCs traveling and cause some WBCs retained indefinitely. Low temperature causes fluid leaking to the affected alveolus and hinders oxygen-carbon dyoxide exchange. Reduced oxygen delivery causes lung vessel vasodilation [23] and make the situation worse. Low temperature also adversely affects the lungs by influencing blood viscosity. For a segment of capillary, its vascular resistance can be determined by equation $R = 8\eta l/\pi r^4$. If a large number of WBCs is in the blood, they raise local vascular resistance. If one or more WBCs are retained in the capillary or move too slowly along the capillary pore, the bulky fluid of blood has to squeeze though the void between the surface of retained WBCs and the capillary wall. Low temperature can cause interstitial pressures to change from negative to positive and promote blood leakage into alveoli. Low temperature may cause the critical time of damage to arrive earlier.

When infection and low temperature work together, they can cause more severe damages to alveoli by reversing the interstitial pressure and raising the capillary pressures. Red blood cells count, platelets aggregation degree, and natures and amounts of other materials affect blood viscosity and thus the pulmonary vascular resistance and the speed of damages.

5. Further lung damages induced by insufficient lung function

If the lungs are unable to perform required functions, degraded energy metabolism leads to diminished lung function and leads to failure of major organs such as heart, kidneys, and liver. Those processes are shown in Figure 2.

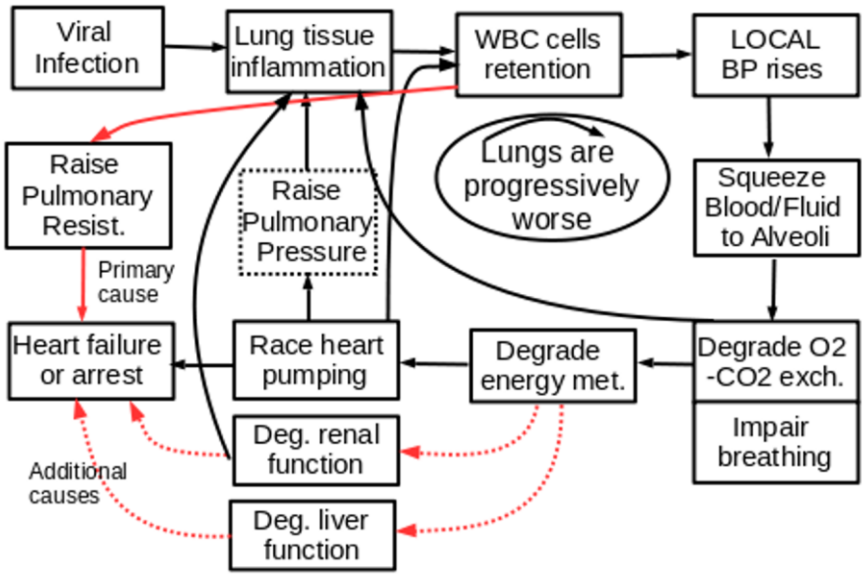

Figure 2 shows how viral infection triggers the retention of WBCs and causes damages to alveoli as indicated by the big round circle. The damages to alveoli results in higher pulmonary vascular resistance and degrade energy metabolism. The increased resistance and impaired heart, renal and liver function inevitably result in heart failure (as indicated by red arrows).

Virus-caused inflammation diminishes lung functions [3, 4], and causes the lungs to fail to deliver required oxygen for the body. The insufficiency of oxygen may cause heart failure [3, 4] and impair renal function [24, 25]. The impaired renal function in turn adversely affects the heart [25, 26] and the lungs [27, 28]. By going through those vicious cycles, the viral infection has an effect of retaining more WBCs in the tissue, retaining more metabolic wastes, and causing more damages to lungs, heart and kidneys. The usable functional capacities of heart, kidneys and liver determine the body's ability to resolve inflammation. It is possible that some patients die from organ failure caused by the vicious cycles even before the lungs have reached the critical point of breaking blood vessels if the patient organ reserve functions are very low.

Serious lung damages could be caused by viral damages before the start of adaptive immune responses. This may happen because low temperature causes blood vessels and capillaries to constrict and raises blood viscosity [13]. The proposed mechanisms also explain the effect of humidity on the disease [14]. When air humidity is high, water molecules coming from alveolar space are not brought out efficiently. The water layers on alveolar walls is expected to interfere with oxygen-carbon dioxide exchange. The mechanisms can explain the role of blood viscosity, mechanical vibrations, etc. Objects jammed at a bottleneck of a bag can be facilitated by making mechanical vibrations. The mechanisms also explain why old people are more vulnerable to the virus. Old people have diminished organ capacities [10, 11, 12] and their blood vessels are less elastic. For people with little heart surplus function capacity, heart failure and death may occur before the lungs are damaged. The mechanisms also explain the role of chronic stress and emotional distress on disease outcomes [16-22]. When the patient is in a relaxed state, the pulmonary vascular circulation is improved and WBCs encounter less friction.

B. Driving Force and Selectivity in Leukocyte Recruitment and Migration

Our proposed lung damage mechanisms add more variables to classic leukocytes recruitment theory. Unlike mobility in bacterial chemotaxis, mechanism by which leukocytes physically move is unclear. T and B cell homing and transendothelial migration have been extensively studied [29]. How neutrophils get activated in a proper way and degree so that they can adhere to the endothelial surface, locomote to right localities and squeeze through small pores is not understood [30]. Further, no directional signals have been found to cause leukocytes to move to the inflammation site [29]. The existing leukocyte recruitment theory can explain that an inflamed tissue selectively retains leukocytes in great details, but could not explain why blood exudates are found in alevoelar spaces.

It is believed that leukocytes take the "path of least resistance" across the endothelium [31]. That means that leukocyte migration path through the intercellular space or through cells may depend on the relative tightness of the endothelial junctions and the ability of the leukocyte to breach them. Existing theories do not use local blood pressures as the driving force. We found that elevated blood pressure or pressure gradient, and structural strength in capillaries or interstitial spaces are determining factors.

Some studies have investigated hydrodynamic properties for leukocytes migration. Models they used involve cancer cell culture media [32], adhesive rolling of deformable leukocytes over a coated surface in parabolic shear flow in microchannels [33] or a simple hydrodynamic model [34]. Those models do not mimic the structures of lungs and do not consider blood pressures in capillary networks in the lungs. One study implies that cell deformability significantly reduces the flow resistance and that high cell concentration is shown to increase the flow resistance [33].

Erratic and uncontrolled leukocyte migration and accumulation were seen in diseased tissues such as atherosclerotic plaque [35] and rheumatoid arthritic tissue [36]. Anti-inflammatory drugs have been used to reduce leukocyte recruitment [37]. Those findings as well as personal observations all show that WBCs are accumulated on a tissue that is inflamed. The whole body tissue is like a big filter from which the blood passes through, and WBCs pass through the filter in a steady state condition. Whenever any specific part of the tissue is inflamed, this part of the tissue will selectively retain WBCs by increasing flow friction. This may be intended by the evolution design to increase dwell times for WBCs to perform their functions at the inflamed site. Leukocytes horizontal migration may be limited to diffusion and the need to find the paths with the lowest flow resistance, but is not necessary. When the blood keeps feeding the WBCs, WBCs must reach wherever inflammation has happened. However, since blood flow can have various patterns, the WBCs may travel accordingly. Inflammation may create an impression that WBCs can be recruited in directions inconsistent with blood flow directions. Since blood constantly supply WBCs to the tissue, there is no need to recruit WBCs from neighbor tissues in a direction perpendicular to blood flow direction. To prove WBCs directional migration, one would need to label specific cells, study the exact traveling paths of the labeled cells, and determine flow directions or the least resistance paths. It would be a great challenge.

C. Implications of the Lung Damage Mechanisms

Maintaining pulmonary vascular circulation is the top priority in the entire disease course for COVID-19 as well as other lung infection. Maintaining the mobility of WBCs is vital important to both innate immunity and acquired immune response [39-41].

Temperature regulates immunity by multiple ways [42]. "Hyperthermic temperatures, heat shock (42°C for 15 min) has been found to blunt leukocyte adhesion within vessels if administered 2 day prior to the intravascular delivery of the neutrophil attractant FMLP in vivo [43]. Moreover, hyperthermic temperatures affect function of all types of cells include DCs, macrophages, NK cells, neutrophils, T and B lymphocytes, and vascular endothelial cells. The picture that emerges is one in which fever temperatures serve as a systemic alert system that broadly promotes immune surveillance during challenge by invading pathogens [42]. Body temperature is controlled by substance interleukin-1 (or leukocyte pyrogen) in the hypothalamus of the brain. Interleukin-1 is released from blood leukocytes and tissue macrophages that have digested viruses and bacteria [8]. Raising temperature in the fever range is a way of improving immune functions.

Raising body temperature can help improve pulmonary micro-circulation and keep WBCs transport balance. Patients should be advised to avoid exposure to low temperature and high humidity in the entire disease course. Other measures should be taken to reduce blood viscosity. We question the measure of using drugs to lower body temperature as standard of care simply because patients demand comfort. Excessive fever can cause damage to the Central Nervous System. A better strategy is maintaining the body at a higher temperature but lowering the head's temperature by using a cooling bath.

Antiviral drugs are effective in the early stage when the functions of major organs are strong. When virus has infected the whole lungs and the patient's lung function has approached a disability level, such a drug may only burden the lungs by its side effects. Long term strategies include reducing tissue inflammation [37], reducing vascular resistance, keeping renal function of removing metabolic wastes and strengthening other vital organs. Medicine should explore drugs that can dilate blood vessels that can be used to reduce the rate of WBC retention.

From the proposed mechanisms, we should see that age, obesity, and organ usable functions are the most important factors. Age is related to organ reserve [10-12]. However, functional reserve may include functions that are not presently useful so that we use organ usable function capacity. When a person's lung usable capacity has little surplus capacity, the infection can more likely cause the lungs to enter the rapidly self-degrading cycle. Obesity is most important factor because that extra tissues have used up compressible volume inside the thorax cage. The severity of obesity is generally indicated by a large size of abdomen. However, extra tissues cannot grow out in the thorax because all ribs are not extensible. This implies that some extra tissues can grow only within inner thorax cage. This is why shortness of breach is a common sign of obesity. The extra tissue caused by obesity necessarily raises the demand for organ functions, and reduce surplus functional capacities of all vital organs. Thus, we found that losing body extra weight is the most effective strategy to increase chances to survive from the pandemic. Nutrition and toxic substances are presumed to influence lung's ability to withstand virus-induced lung damages by affecting innate immunity and adaptive immunity response.

Sequential leukocyte rolling, adhesion, and trans-endothelial migration constitute a complex multistep paradigm that is orchestrated by multiple adhesion molecules [4, 44]. Moreover, WBCs and compounds must interact in blood while they also interact with molecules exposed on contact surface

of tissue. The effects of adhesion molecules may vary in different persons, and molecular interactions are not the focus of the present study. If the mechanisms do not explain outcomes of certain persons, most probably reason is that their pathological processes are significantly or primarily controlled by molecular interactions.

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CONFLICT OF INTERESTS

None

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Supplement To Two-Phase Lung Damage Mechanisms For COVID-19 and Other Viruses

A. Compressible Volume of Lungs Taken by WBCs at Various Times

Table S1 Percent of Lung Compressible Space Filled By Blood Exudate Increases with Time (based on cell volume)

Ret. WBCs (/min)	Cell Vol. (cu. μm)	Ret. Rate (mL/min)	Time (mins)	Time (hours)	Exudate Vol. (mL)	Per Cent of Def. Vol. (%)
35000000	1000	0.035	1	1 min	0.035	0.00175
35000000	1000	0.035	60	1 hour	2.1	0.105
35000000	1000	0.035	1440	1 day	50.4	2.52
35000000	1000	0.035	7200	5 days	252	12.6
35000000	1000	0.035	14400	10 days	504	25.2
35000000	1000	0.035	28800	20 days	1008	50.4
35000000	1000	0.035	43200	30 days	1512	75.6

The discrepancy between the two methods is attributed to the approximate volume of WBCs and estimated mean WBC cell volume. The absolute numbers are unimportant because such data cannot be applied to any specific person. When the lungs cannot maintain WBCs transport balance, the lungs may fail within five to ten days. If the retention rate of WBCs increases to 1%, the patient may die in one to two days. This may happen when a big part of alveolar spaces are filled by extruded blood and leaked liquid .

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