Hypothesis



# Long COVID: A Chronic Shortage of Blood. A Treatment Proposal Based on Reasoned Speculation from Pathophysiological Principles

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# Long COVID: A Chronic Shortage of Blood. A Treatment Proposal Based on Reasoned Speculation from Pathophysiological Principles

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**Abstract:** The signs and symptoms of Long COVID can be explained by a shortage of blood in the body and a resulting deficient blood flow through nearly all organs. This shortage arose during the acute phase of COVID19 by an increased breakdown of haematocytes, to which the liver responds by reducing the production of albumin, in order to prevent a too large decrease in haematocrit. In order to ensure the perfusion of organs that are directly necessary for survival, the body takes the emergency measure of diverting blood from other organs and tissues. The perfusion of the blood-producing organs is also affected by this distribution measure, which hinders the smooth recovery of the total blood volume. The body is stuck in this vicious circle: a shortage of circulating blood hinders the recovery of blood production. This explains the long duration of Long COVID. My proposed treatment of Long COVID focuses on the recovery of the correct volume of blood in the body of the right composition by the intravenous administration of donor blood products, starting with albumin concentrate. A trial treatment can be performed in any hospital without much additional preparations, and has a lower associated risk for the patient than analysing the total blood. A diagnosis *ex juvantibus*, by therapeutic response, is therefore preferable, and will result in the healing process starting earlier. I suspect that most Long COVID patients will exhibit a high serum ferritin level as a result of internal haemolysis, and haematocrit and albumin values at the high and low extremes of the reference range because the liver can not keep up with the recovery of the red bone marrow.

**Keywords:** blood volume; allocation of blood flow; arteriolovenous anastomosis; venous blood buffer; vascular constriction; blood osmolality; haematocrit; albumin; ferritin

## The Plausibility of a Shortage of Blood

The pulmonologist does not find any abnormalities, neither in X-ray investigations, nor in functional spirometric investigations.

My granddaughter who is 28 years old became severely ill with Long COVID following acute COVID-19 mid December 2022.

When I saw her again after some time, I was shocked by her severe pallor. I had never seen anything like it in my 36 years as a general practitioner, and I initially thought of a serious case of anaemia. A few days later she presented blue nail beds which does not support the diagnosis of anaemia, as the blood apparently does not have a shortage of colour. This gave me the idea that flow of blood is squeezed as a response to a shortage of blood.

So the blood does not lack colour, the body does lack blood.

All signs and symptoms of Long COVID patients can be explained by a (varying) poor perfusion of many tissues and organs by a shortage of blood, and a distribution of the remaining blood. As in the case of my granddaughter:

- Occasional extreme pallor:
  caused by narrowing of the subcutaneous veins. This is a strong indication that the venous blood buffering capacity has been drained as an initial compensation for a shortage of blood.

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- Occasional blue nail beds:
  caused by a fluctuating arterial blood flow to the skin.
- Fatigue and slow recovery after minimal exertion of muscles and brain
  (Post-exertional malaise, PEM):
  caused by inadequate removal of waste products due to insufficient flow of blood.
- Strongly increased pulse rate when standing
  (Postural orthostatic tachycardia syndrome, POTS):
  because the heart is not sufficiently perfused it can only provide the increased energy requirement when standing by increasing the pulse rate. .
- A heavy feeling in the arms and legs:
  caused by insufficient blood flow to the muscles that require constant perfusion, even at rest, for the maintenance of motor end plates, tendon attachments, and muscle cells.
- Hypersensitivity to light and sound:
  caused by insufficient blood flow to the sensory organs.
- Pain throughout the entire body:
  caused by insufficient blood flow to peripheral nerves.
- Periods of not being able to move at all:
  caused by insufficient blood flow somewhere in the central nervous system.
- Reduced tolerance to heat:
  caused by insufficient blood flow causing a reduced ability to lose heat by radiation or sweating.
- Dyspnea:
  because of the large shortage of blood there is insufficient blood for gas exchange sometimes even in rest.

Research has found small blood clots in the capillary networks of all organs (*1*). However, the insufficient circulation can not solely be explained by permanent blockage of the capillaries because the severity of the symptoms varies throughout the day, such as in the case of periods of not being able to move at all. These varying symptoms *can* be explained by a varying blood flow to the associated capillary networks. The change in blood flow to these capillary networks can be regulated in two ways: Firstly in an autonomous manner by the organ itself through the closing and opening of the passage gates between the arterioles and the capillaries, and, secondly by signals from other organ systems that overrule this first mechanism, causing the arterial blood to be directly redirected to the draining veins via the arteriolovenous anastomoses, bypassing the capillary network.

The inflammations in the brain that were found in a number of long COVID patients (5) can also be caused by insufficient perfusion. Blood flow is not only necessary for the supply of nutrients, oxygen and other compounds but also for the removal of protein breakdown products from normal cellular metabolism. The stagnation of this removal can trigger inflammatory processes.

In research on the blood laboratory values of Long COVID patients it was found that *all* patients had high serum ferritin levels (*6*). This indicates that there is a reduced production of erythrocytes, because under normal circumstances the iron that is released by the breakdown of erythrocytes is immediately used in the production of new erythrocytes. If the production of erythrocytes stagnates, the iron released in the breakdown of erythrocytes is stored in ferritin, particularly in the cells of the liver, and also leads to an increased serum ferritin level.

The symptoms of Long COVID present themselves as a form of chronic fatigue syndrome (*1*). It has already been shown by measurements that this syndrome is associated with a shortage of blood in the body (*7*,*8*). But a good explanation and a treatment based on it have until now not been developed.

Since the invention of aspirin, medical research is mainly focused on molecular enzymatic processes in the tissues, this has yielded good results, but the cause of this disease lies at the level of interacting organ systems and that is where therapy should focus in this case.

**How the Shortage of Blood Comes about**

Which cells are prey to the virus?

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During the haematogenous spread of the virus in the acute phase of COVID-19, virus particles are rapidly spread via the arteries through the entire body. They adhere to the endothelial cells that form the inner lining of all blood vessels. This adhering particularly occurs in those areas where the speed of the flow of blood is significantly reduced: in the capillaries of all tissues. Like all other cells, endothelial cells have ACE-receptors that are used as a gate of access by the virus (the endothelial cells are not good host cells for the virus, and are therefore not a source of new virus particles).

As a result, everywhere in the capillaries endothelial cells are destroyed, which leads to leaks in the walls of the blood vessel, in which blood platelets are activated. Clots of erythrocytes and fibrin are formed.

Such a capillary is thus completely disabled. This impedes blood flow and, consequently, the function of the tissues and organs, including the haematopoietic organs (*4*). Due to the many capillaries being disabled, the total flow capacity of the blood vessel network is greatly reduced, and the normal amount of blood has become too large, relative to this flow capacity. This "surplus" of blood is taken up by the venous reverse capacity.

Red blood cells that are not captured in these clots are damaged by their passage along damaged endothelium and are then quickly eliminated by the spleen.

The normal breakdown of red blood cells continues as normal.

These processes lead to a large reduction of the total amount of red blood cells.

The liver responds to this by reducing the production of albumin, in order to prevent a too large decrease in haematocrit, the kidneys excrete the water which has now become superfluous, and the haematocrit level is back to normal.

In blood tests, one finds a normal haematocrit level, but the total amount of blood is reduced.

The long COVID patient has an insufficient amount of blood to perfuse all organs according to their needs.

**The Distribution of the Remaining Blood**

In response to the shortage of blood, the vascular system reduces its calibre and decreases its metric volume. This is done by the veins which have to adapt daily to changes in requirements of circulating blood, for example in order to adapt to the differences between lying and standing, and a warm and a cold environment. The buffer capacity of the network of blood vessels lies mainly in the veins, which can shrink without initially increasing their pressure. It is only when the venous buffer capacity has been maximally used that there is not enough blood available to sufficiently perfuse all organs to their requirements at the same time, and a distribution of blood will be necessary. In order to sufficiently perfuse organs that are directly necessary for survival, the body takes the life saving emergency measure of diverting blood from other organs by opening their arteriolovenous anastomoses. Under normal circumstances, an organ autonomously regulates the flow of blood through its capillary networks according to the variable needs of the moment. In the case of a blood shortage, however, the organism as a whole overrides this mechanism.

The organ systems that are directly necessary for immediate survival of the organism need constant perfusion and are therefore spared as much as possible. These include:

- the muscles necessary for breathing: the intercostal muscles and the muscles of the diaphragm
- the brainstem, spinal cord, and nerves that control the muscle groups mentioned above.
- and of course the arterial blood supply to the heart muscle itself.

The blood flow to the lungs is a separate story because the total amount of blood that flows through the entire body in one minute must also flow through the lungs in its entirety within one minute. In healthy individuals, particularly in rest, the arteriolovenous anastomoses in the lungs are wide open because much more blood is continuously supplied than is necessary for the gas exchange. Because of this, the blood is directly siphoned through the pulmonary veins to the left part of the heart. In long COVID patients, these anastomoses are for a large part closed, even in rest, in order to let the small amount of blood flow through the capillary nets of the lungs.

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A seriously ill Long COVID patient cannot afford even minimal exertion (3) because the total amount of blood is quickly insufficient to maintain an acceptable level of central circulation. Additionally, there is not enough blood available to clear the metabolic waste products after exertion.

The live-saving emergency measure of the organism to distribute the blood impedes the recovery because it also reduces the perfusion of the liver and the red bone marrow that need to produce new blood.

**Stagnation of Recovery**

After the virus has run its course, the recovery process can begin.

The formation of new capillaries becomes greater than their demise. There is again more space for blood. The liver and kidneys together produce more plasma, and the red bone marrow can release more red blood cells.

The spontaneous recovery comes to a halt when either one of these haematopoietic organs does not produce its blood components in pace with the other. If there is not enough plasma, the production of erythrocytes by the red bone marrow halts, and conversely, if there are not enough erythrocytes, the liver has to decrease the production of albumin. The organism is focused on maintaining both the albumin and the haematocrit values within the reference range:

- If the haematocrit would drop too low, the oxygen-carrying capacity of the blood that flows through the tissues would become too low, and if the haematocrit would become too high, the blood would become too viscous which would impede its flow.
- If there is too much plasma, the blood would become too thin, and then too few erythrocytes would pass through the capillaries of the liver per unit of time, which would reduce the gas exchange in the cells and thereby also the production of albumin, among other things. If the albumin content of the plasma falls below the reference value, more pre-urine is produced and the kidney then excretes the excess water to maintain the colloid osmotic pressure, and thus the plasma quantity becomes smaller.

As an example of laboratory blood values with haematocrit at the extreme highest end of the reference ranges and albumin at the lowest end of the reference range, consider those of my granddaughter (Figure 1):

| | | | |
|---|---|---|---|
| Albumine | 35 | gr/L | 35 - 55 |
| Hemoglobine | 9.7 | mmol/L | 7.5 - 9.7 |
| Hematocriet | 0.46 | L/L | 0.35 - 0.47 |
| Erytrocyten | 5.19 | x10^12/L | 3.80 - 5.20 |

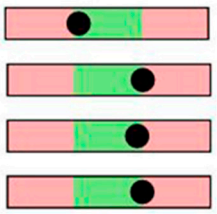

**Figure 1.** laboratory blood values measured in my granddaughter, albumin is at the lowest end of the reference range, and haemoglobin, haematocrit and erythrocytes are at the highest end of the reference range.

This situation indicates that the production of albumin cannot keep up with the production of red blood cells. This causes both to stagnate. The liver is apparently unable to respond sufficiently to an increase in haematocrit, and can keep the amount of albumin at the required level only for a smaller volume of plasma, and sometimes even only just with an albumin level in the plasma at the low end.

An explanation of why the recovery of the liver lags behind the recovery of the red bone marrow is that the liver, in addition to arterial blood, is also perfused with blood from the portal vein coming from the intestinal mucosa, which contains less oxygen, more carbon dioxide and more viral particles (2). The liver is thus attacked by the virus from two sides: not only from the primary foci in the lungs but also from the secondary foci in the capillaries of the intestinal mucosa. Therefore, the liver has (had) a greater viral load than the bone marrow.

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I suspect that we will find a high haematocrit and a low albumin level in most Long COVID patients before the start of the treatment, because the liver cannot keep up with the recovery of the red bone marrow.

**Proposed Treatment**

The treatment aims to break the vicious circle: a shortage of circulating blood hinders the recovery of blood production.

We achieve this through the intravenous administration of donor blood plasma in the form of albumin concentrate.

If the therapy is successful, the serum ferritin level will decrease.

The patient who uses enzyme inhibiting drugs must stop taking them because these drugs also hinder healing processes such as the production of albumin in the liver and the new growth of capillaries, which we must promote.

So do not use:

- anti-inflammatory pain-relieving medications, which are prostaglandin inhibitors, such as aspirin, ibuprofen, diclofenac and even paracetamol
- proton pump inhibiting antacids (replace if necessary by gastric acid-binding compounds).

This treatment can only take place in a facility that is equipped and qualified for blood transfusion, under the authority of a physician familiar with blood transfusion.

When performing blood transfusions on Long COVID patients, we pay attention to the following:

- The infusion must not be prepared with, at least the patient is not left with, a saline infusion because the colloid osmotic pressure of the blood may be critically low.
- The infusion must be administered very slowly and with small amounts per day to allow the osmotic pressure to adjust and because the potentially stiff blood vessels cannot adapt quickly. The entire vascular system needs time to adapt. If it goes too fast, the blood circulation in the lungs will be overloaded.
- There must be continuous supervision by a qualified physician or nurse to stop the infusion if the patient becomes short of breath.

A therapeutic period could consist of one or two sessions per day with the well-being of the patient as the guiding principle.

The treatment is stopped when the patient feels healed.

If after a number of sessions it appears that the patient does not benefit from it, the following sessions are cancelled.

Prior to the first session, haemoglobin, haematocrit, serum albumin and serum ferritin must be measured. The values found are evaluated with consideration of the patient's stature and sex. Patients with a low serum ferritin level have to be examined for occult blood loss.

We will start with an infusion of albumin:

- Dose of albumin concentrate per session: equivalent to 100 mL of plasma as in a vial of 100 mL with an albumin concentrate of 40 g/L.
- Infusion rate: 1 mL per minute.

If prior to the next session the Hb (by proxy for the haematocrit level) is not on the low side, we can continue giving albumin concentrate because the red bone marrow has responded by releasing more red blood cells.

If, on the other hand, the haematocrit is on the low side, we wait for one to several days to see if it will rise.

If the haematocrit does not increase, there is an apparent stagnation of the erythrocyte production, I hope and expect that this will not happen often.

In that case we check whether the serum ferritin has decreased, in that case a cautious administration of erythropoietin (and/or another growth factor) may be considered to stimulate the red bone marrow.

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If the serum ferritin becomes too low (< 80 µg/L?) and the haematocrit does not rise, erythrocyte concentrate or whole blood from a donor may be considered.

Everything based on the clinical picture, the well-being of the patient and the common sense of the doctor.

This treatment proposal does not (yet) claim to be based on clinical evidence but is based on reasoned speculation: the projection of the symptoms of Long COVID onto the structure and functions of the human body.

Which qualified physician will offer my granddaughter a trial treatment?

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