

Successful Treatment of Long COVID Patients by Means of HELP (Heparin-mediated Extracorporeal LDL Precipitation)- Apheresis

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Abstract

BACKGROUND

10 -30% of COVID infected patients develop a chronic state of disease that hinders them for months to recover due to severe persisting pulmonary, neurologic, cardiac, and other deficits. A key mechanism of COVID infection is sought to be a systemic endotheliitis and microembolization affecting various organs. Thus, an extracorporeal method like the HELP-apheresis able to remove clotting factors, endotoxins and inflammatory mediators might be useful to restore vascular homeostasis in persisting COVID infection. (see Article 2)

METHODS

We randomly assigned 18 long-covid patients to receive repeated HELP-treatments in short intervals (1-8 sessions) until they recovered from major clinical symptoms.

RESULTS

Of the first 18 patients treated, 17 patients sustainably improved in their clinical well-being, whereas one patient did not experience a relief of symptoms: 9 patients fully recovered after 1 – 3 treatments, whereas 8 patients required 3-8 treatments to improve.

CONCLUSIONS

Of the 18 patients with severe long-COVID symptoms, 17 had experienced a great benefit. One did not profit, although his oxygen saturation ameliorated. HELP-apheresis provides a promising safe treatment option for long-COVID patients.

Case Reports

1. 30-year-old caregiver, Krupp Hospital, Essen, infected 11/2020 while on duty in the Corona ward (first positive SARS-CoV-2 smear: 11/24/2020). Previously, the man was healthy and athletic. In 2017, he contracted pneumonia, which healed. During quarantine developed fever and complete exhaustion, barely able to make it from bed to kitchen. Later developed severe course of disease with protracted dyspnoea. This prevented him from climbing 20 steps without becoming short of breath. On 12/20/2020, he took his first walk but had to stop after 50–60m. On 02/02/2021, received first of three HELP apheresis treatments (02/10/2021,02/16/2021). After 1st apheresis, was better able to breathe and walk >40 steps relatively quickly, although his breathing rate still accelerated. After 2nd apheresis, completely symptom-free the day after, discontinued the medication with salbutamol spray. Two days later, able to jog 20km again. Thoracic CT showed complete healing with no residuals; this continues to this day.
2. 24-year-old overweight caregiver became infected in Dortmund municipal hospitals in 11/2020. Before the infection, regularly did strength and endurance sports, played football. Arterial hypertension was treated with ramipril. Positive swab for COVID-19 on 11/16/2020. 7h later, developed strong feeling of illness. Pulse rate increased to 140 bpm, developed elevated temperature and lost his sense of taste/smell. He slept on a floor because he lacked the strength to walk back to bed. For 7 days, his body temperature remained at 39.2°C and then dropped to 37.2°C. He took paracetamol. Main symptoms: complete exhaustion, diarrhoea, shortness of breath during any lightest physical

exertion. His GP administered ampicillin 8g, dexamethasone and heparin for 12 days. A thoracic CT on 12/05/2020 revealed no pathological findings. He spent sleepless nights. Resumed his duties but was unable to climb 2 floors without air hunger. Two HELP apheresis treatments at intervals of 3 days (date: 03/09/2021 and 03/12/2021) meant he was also symptom-free on the day after the second apheresis and was able to resume his sporting activities to full extent till now.

3. 53-year-old nurse with post-acute COVID syndrome, infected in a care-home service in Bochum 02/2021. Suffered from bronchial asthma and mitral valve insufficiency since childhood. COVID infection initially caused severe headaches, persistent fever of 40°C, fatigue and shortness of breath at slightest exertion, severe pain in both legs. She had fluticasone/vilanterol spray. A pulmonary CT revealed a lung infarction (scarring and calcifications). She reported severe concentration problems which lasted (>a month) without improvement. After 1st apheresis on 03/30/2021, she felt a slight improvement. The day after 2nd apheresis, 04/06/2021 she felt unwell: describing an altered body awareness. After 3rd apheresis on 04/20/2021, she experienced a breakthrough during apheresis: able to breathe deeply and freely again. Later, physical resilience increasingly improved, could go for walks again; not only on an even surface but also inclines. The discomfort in her legs was also less severe.
4. Husband of the third patient, 58-years-old tested positive for COVID-19 as part of a planned cataract surgery in 02/2021. Diagnosed with prostate carcinoma in 2018. During acute COVID infection developed fever, cough, massive headache, pain in limbs "like rheumatism in terminal stage". He felt tired and

weak continuously, complained of sentence breaks, forgetfulness, unable to breathe deeply, lung function was limited. After 1st apheresis on 03/30/2021, reported improved concentration and fewer breaks in his speech. After 2nd apheresis (04/05/2021), reported a “bad body feeling”, one day later; however, this had disappeared. Reported a noticeable improvement in neurological limitations. After 3rd apheresis on 04/20/2021, both neurological deficits and shortness of breath were massively alleviated. Sense of smell recovered only partially: e.g. could smell vanilla but not lemon. After two further apheresis treatments on 06/01/2021 and 06/06.2021 his venous oxygen saturation prior to treatments stabilised around 80%, and increased as compared to the previous treatments being only 63%, 70% respectively.

5. 56-year-old pharmaceutical scientist, infected in the first wave during holiday in Ischgl/Austria on 03/2020. After acute phase with fever, complained mainly of severe dyspnoea lasting for months with cough, poor resilience, severe concentration disorders, memory lapses, sentence interruptions, temporary paralysis, skin symptoms on hands (blisters and peeling skin). During and after first of the three HELP apheresis treatments (03/30/2021, 04/06/2021,04/15/2021), she was able to breathe more freely, concentration improved. After 2nd apheresis, she felt “like reborn”; symptoms improved. Skin symptoms healed. After 3rd and 4th apheresis, completely recovered and could ride horses and play golf again, without shortness of breath. Ability to concentrate was also much better till now.
6. 30-year-old heating engineer from Bottrop. Infected with COVID 05/2020 and in hospital for suspected myocarditis, complained of very severe headaches, loss of sense/ smell lasting 6 months and persistent weakness in performance.

Symptoms disappeared completely after HELP apheresis was carried out on 04/12/2021 until today. A thoracic CT revealed no pathological findings except for low-grade ventilation disturbances.

7. 32-year-old architect from Gelnhausen with arterial hypertension, slightly overweight but athletic. After COVID infection in 12/2020, initially developed severe headaches, dizziness, earaches, shortness of breath and angina pectoris, which lasted > 14 days. He could walk only 200m before having to stop and rest. He felt “endlessly limp” and was unable to work under pressure. Admitted to the Main-Kinzig-Klinikum as an inpatient 03/23/2021. Cardiac MRI revealed perimyocarditis with fibrosis, scarred areas subepicardially, pericardially-laterally and inferolaterally. In parallel, developed weakness of right leg, which he dragged. Head MRI revealed two lacunar defects (medullary camp frontally left). On 04/06/2021, 04/12/2021, 04/23/2021, performed three HELP apheresis treatments. During 1st apheresis, felt angina pectoris again, afterwards felt clearer in head and less in need of air. After 2nd apheresis, symptoms improved dramatically: headaches subsided, was able put much more strain on himself, even jogging. His gait was clearly better. A parallel rehabilitation also helped. After 3rd apheresis on 04/23/2021, he could return to his former life.
8. 53-years-old head physician of a rehabilitation clinic from Soest. Before he contracted COVID in 01/2021, he could walk 50km and practised sports. Initially, experienced flu-like symptoms of infection up to 39.3°C with a wave-like course and non-productive cough. His resilience was clearly limited, climbing stairs caused shortness of breath and thoracic pain on deep inspiration. Anosmia and headache were present only initially. Suffered daytime fatigue and concentration problems, restless legs and gastrointestinal

irregularities. A pulmonological examination 02/10/2021 revealed no damage to lungs. Head MRI revealed no abnormal findings except for bifrontal medullary gliosis and an arachnoid cyst. Patient described it as follows: "No longer able to strain himself and unable to concentrate and work >4 hours. After mowing his lawn, he was 'half-dead' and rested 3 days. After three apheresis treatments on 04/12/2021, 04/15/2021, and 04/20/2021, he reported significant decrease in all symptoms and striking improvement. Overall, he received 7 treatments which allowed to return to full work.

9. An anaesthetic nurse from Krupp Hospital, Essen. Infected in the operating theatre. Tested positive 12/2020. Previously suffered depressive episodes. She infected her children and her mother, who developed an ARDS syndrome and became chronically hemodialysis dependent. Initially, she experienced headaches, loss of smell/taste, and appetite, difficulties in thinking and concentrating, persistent air hunger when climbing one floor of stairs. Also reported skin rash, hair loss and black streaks in her nails (possibly embolic). We performed three HELP treatments (04/13/2021, 04/16/2021, 04/22/2021): after 2nd apheresis, she felt clearer and could breathe better. Further treatments were performed 04/29/2021, 05/04/2021, 05/11/2021 and 06/02/2021. After 4th apheresis her articulation facilities and memory improved markedly. Sense of smell and taste recovered partially. She could climb more steps and felt less depressive. By end of June rehabilitation starts because persisting single days with headaches and memory problems, although much attenuated.

10. 35-year-old firefighter from Neukirchen-Vluyn, contracted COVID-19 on 10/2020. Initially had fever up to 40°C for 6 days; after speaking only three words, started to feel short of breath. His lips became cyanotic, experienced

repeated hypertensive crises, 60bpm at rest, (twice presyncopal). The performance deficit persisted. Before COVID, he reported pedalling 270watts on the ergometer and regularly jogging 15–20km, now only 2km of walking. Every night had sleep disturbance, several times had to sit up and gasp for air. The thoracic CT revealed left basal scarring. 12/31/2020 vaccinated against COVID-19 despite infection and worsened. The 1st apheresis was performed on 04/22/2020, he was breathing noticeably better and could sleep through the night again. 2nd and 3rd apheresis 04/27/2021, 04/30/2021 accordingly. Afterwards, could jog for 30min. After 4th apheresis 05/08/2021, could jog 8 km every two days already. Three further treatments 05/17/2021, 05/25/2021, 06/01/2021 let him recover fully and return to work. Arterial oxygen saturation was 98%.

11. 72-years-old a former car mechanic from Mülheim, contracted COVID-19 10/2020. When cold symptoms did not subside after two days of bed rest, his GP admitted him to Mülheim hospital. Next day, was transferred to the intensive care unit because of developed COVID pneumonia with acute respiratory failure. X-ray of 11/02/2020 revealed reduced inspiration and peripherally emphasised infiltrates. He received systemic dexamethasone, intravenous antibiotics with piperacillin/ tazobactam, because of suspected superinfection (without evidence of pathogens). When respiratory insufficiency worsened, he was given oxygen, initially intermittently as non-invasive ventilation then as nasal high flow therapy. X-ray control revealed “a discrete loosening of known infiltration of COVID-19 pneumonia on left side, but essentially unchanged findings”. He remained in ICU for 17 days with persistent hypoxaemia <90% saturation. 11/18/2020, he was discharged with a negative PCR test and prescribed long-term oxygen therapy.

One week after discharge, developed severe lung pain and high pulse rate of >100 bpm. Because of suspected pulmonary embolism he was prescribed apixaban and cortisone. Angio-CT of lungs 02/11/2021 and control CT 03/25/2021 revealed unchanged chronic interstitial pneumonia without lobar pneumonic consolidations (see figure 1).

On 04/27/2021, his 1st HELP apheresis: the blood in tubes appeared almost black, after 300ml, there was a risk of clotting; by adding more heparin, 3l of blood plasma was successfully treated over 4h at a plasma flow rate of 8–13ml/min; before apheresis, oxygen saturation in venous blood was 25.3%. Immediately after apheresis, it was 44.2%. Before 2nd treatment 04/30/2021, venous oxygen saturation was 52.3%. Five days later, oxygen saturation was 58%. On 05/11/2021, oxygen saturation was 80%, on the 05/14/2021- 85% before apheresis. A control CT revealed reversion of pathologic findings. (See Figure 2). Already before, he suffered from Alzheimer's disease, thus he cannot express his condition, instead his wife noticed a favourable improvement in his daily life.

12. 40-year-old physiotherapist, infected in Mülheim hospital ward, tested positive for COVID 01/18/2021. Next day developed headache, ear rashes, circulation collapse, chest pain, cough, shortness of breath and hoarseness, depressive mood and strong fatigue - with symptoms enduring throughout the quarantine. Additionally, she could not read. Two days later, developed a fluttering pulse, heart rhythm irregularities and resting dyspnoea, prominent muscle/ankle pains. Her movements resemble Parkinson's disease together with general weakness and permanently feeling cold. 01/30/2021 her foot and legs felt persistently burning and painful. Plain sunlight caused severe headache. She received five HELP treatments up to now. After 3rd treatment

her freezing fades. Breathing gets easier. Her 4th treatment had to be interrupted because the needle clotted due to a 10cm long intravenous coagulum. The 5th treatment brought the breakthrough: she can breathe and move much better. The paraesthesias in her legs diminish. Physical training gets possible with early pulse fluttering. After the fifth apheresis she can ride a bicycle for 30min. Her concentration improves. Sunlight no longer causes headache. A spirometry test and chest X-ray reveal no pathologic findings. Symptoms almost gone.

13. 50-year-old medical assistant from Erwitte, infected in a rehabilitation clinic 01/10/2021. Developed persisting shortness of breath, fatigue and neurologic problems, especially wording, memory and concentration deficits. We performed three apheresis treatments up to now (05/05/2021, 06/01/2021,06/04/2021), each of which brought her relief in respect to breathing, less coughing, better fitness and less fatigue and better neurologic recovery.
14. 28-year-old lady from Bad Sassendorf, infected on duty as ergo-therapist, tested positive 01/02/2021. Shortly after, developed cough, throat and chest pain which worsened. During quarantine she was unable to climb more than 3 steps without shortness of breath. Lost her sense of smell and taste, had concentration deficits and fatigue, but no muscle or ankle pain. Before her first and single apheresis treatment on 05/04/2021 she could merely climb two floors of stairs. The apheresis procedure had to be stopped after treatment of 1338mL plasma volume because a coagulum had clotted the needle. Nonetheless, after apheresis her symptoms disappeared all except for the still lacking smelling sense. She wanted no second treatment because of becoming pregnant.

15. 63-years-old caretaker from the Ruhrlandklinik/Essen, infected on night duty 04/2020. He had arterial hypertension and hypercholesterolemia. After initial cough symptoms, developed muscle pain and dyspnoea, had massive trouble with short-term memory. Intermittent headaches, concentration problems and dyspnoea persisted over one year. He received 4 apheresis treatments. During 1st apheresis 04/28/2021, venous oxygen saturation increased from 28,8%-72,8%, during 2nd apheresis 05/04/2021 it rose from 48,5%-65,7%, during 3rd apheresis (05/10/2021) it fell from 79,7% to 71,0%, and during last apheresis 05/25/2021 improved again from 43,0%-84,4 %. He could not experience a relief in symptoms. Treatment was stopped because his rehabilitation started.

16. 29-year-old sportive accountant from Hamburg. Tested positive for COVID 03/07/2021. Initial symptoms: total fatigue, fever, coughing and sneezing. Persistent symptoms: loss of sense of smell and enduring lack of power and dyspnoea not allowing any sports. Received 1st apheresis 05/03/2021. Two days after she undertook a walk with her mother when realised that she could smell again surrounding grass and woods. After 2nd apheresis (05/06/2021) she could breathe much better and jog again 3 times per week. After 3rd apheresis (06/07/2021) all symptoms of COVID disappeared until now.

17. 21-year-old, sportive bugler from Saarbrücken, COVID infected since 11/08/2020. Symptoms comprised: fever, muscle/angle pain, headache, coughing and gastrointestinal trouble. Two days later, sense of smell and taste was gone, lungs felt like "full of sawdust". Persisting symptoms: shortness of breath, cough, fatigue, muscle/angle pain making sports impossible and massive concentration problems when playing horn. Three

HELP treatments conducted within one week in 06/11/2021 reversed all symptoms enabling him to jog again and play horn as before.

18. 42-year-old entrepreneur from Nicosia, infected 11/20/2020. After initial cough, fever, hoarseness, headache and spine, muscle, joint pain he lost sense of smell and taste, fingertips burst open, developed depression and severe anxiety, insomnia, night sweats and brain fog. Concentration deficits and extreme fatigue made him bedridden together with post exertional malaise. Developed neurologic problems: wording, short-term memory. Pulmonary gas exchange dropped to 78%. After 1st apheresis, he was rid of all symptoms except short-term memory and concentration deficits. After 2nd apheresis, concentration deficits were gone. After 3rd apheresis, sense of hot/cold and pain returned fully (which he had not recognised as gone earlier). During regeneration, he first felt some minor vein pain and burn, resting pulse was 15-20% higher. Table 2 shows patient became exercise tolerant, oxygen levels fully recovered during rest/exercise, short-term memory improved quickly.

Conclusion

These preliminary observations represent work in progress: improving the microcirculation of long COVID haulers enables restoration of vascular homeostasis. This approach should be considered for treatment of acute severe COVID cases on ICU wards.

Figure 1: Pulmonary CT image (03/25/2021) of patient 11 before HELP treatment

The lung window continued to show a mixed pattern of mosaic-like flat lactic opacities of the lobules with increased interstitial markings in all lung sections, in each case extending into the pleura in the lung mantle with no significant change as compared to the previous CT from 2021.

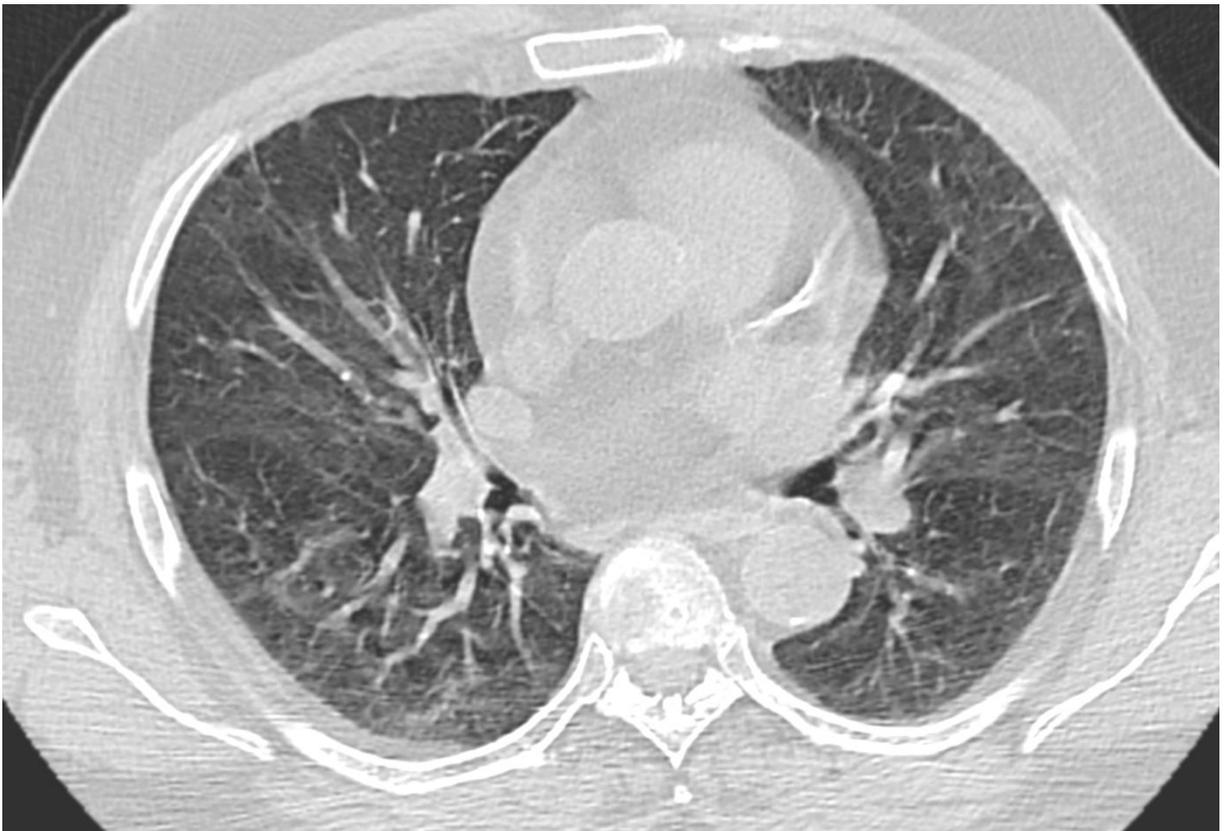


Figure 2: Pulmonary CT image of patient 11 after four HELP treatments.

After 4 apheresis treatments, i.e. 2 weeks later, the lung window shows a dramatic reversion of COVID pneumonia in all lung sections which

corresponds well with the improved oxygen saturation,

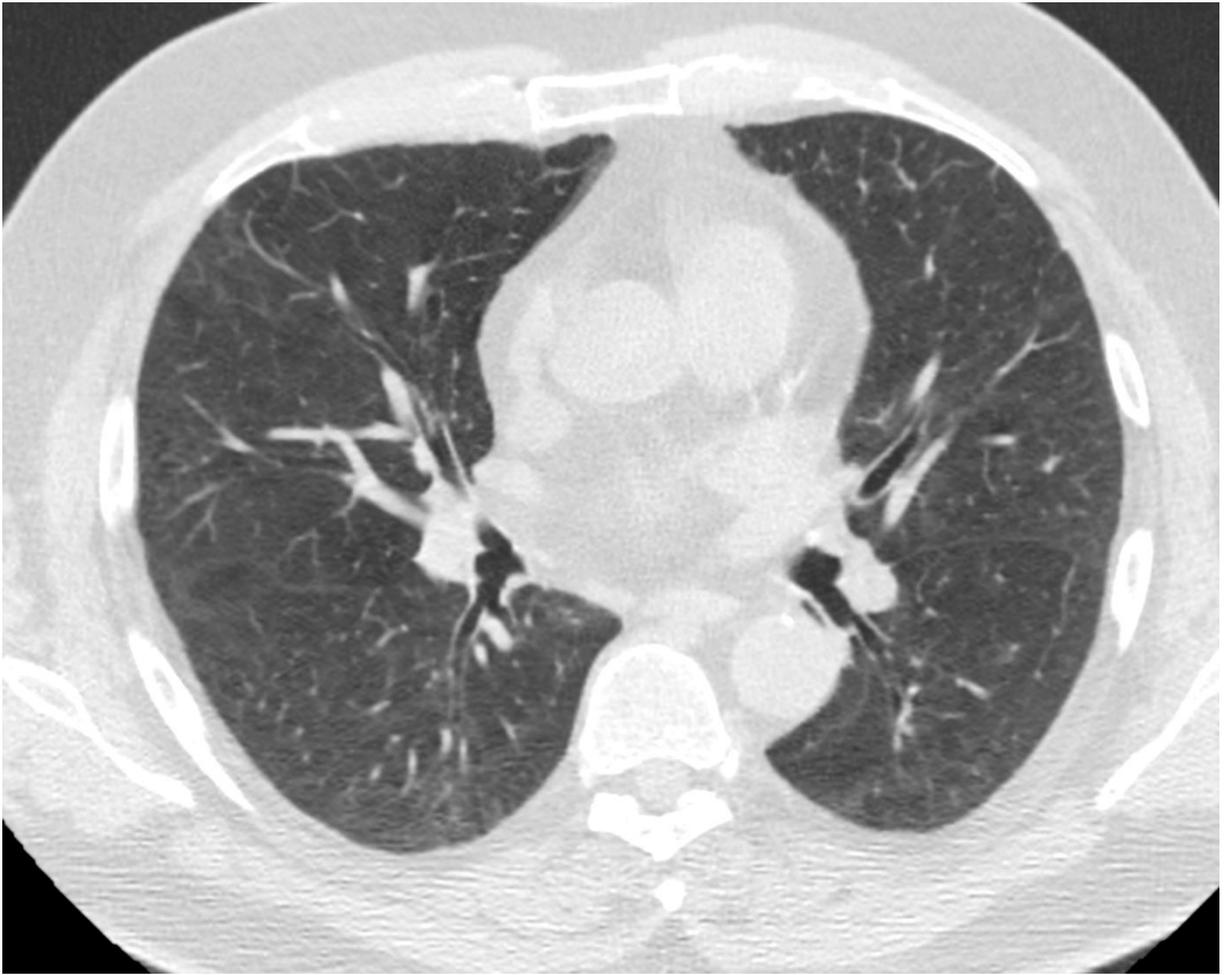


Figure 2.

Table 1. Patient no 18, Pulse and SpO2 data

	Pulse (at rest)	SpO2 (at rest)	SpO2 (after 5 min at 130 Pulse)
17. June	63	90%	n.a. patient could not exercise
18. June (after 1st treatment)	60	94%	85%
19. June	53	93%	87%
20. June	55	93%	87%
21. June (after 2nd treatment)	62	93%	89%
22. June	64	93%	88%
23. June	66	93%	89%
24. June (after 3rd treatment)	64	95%	90%
25. June	54	95%	93%
27. June	56	97%	92%
28. June	55	96%	95%

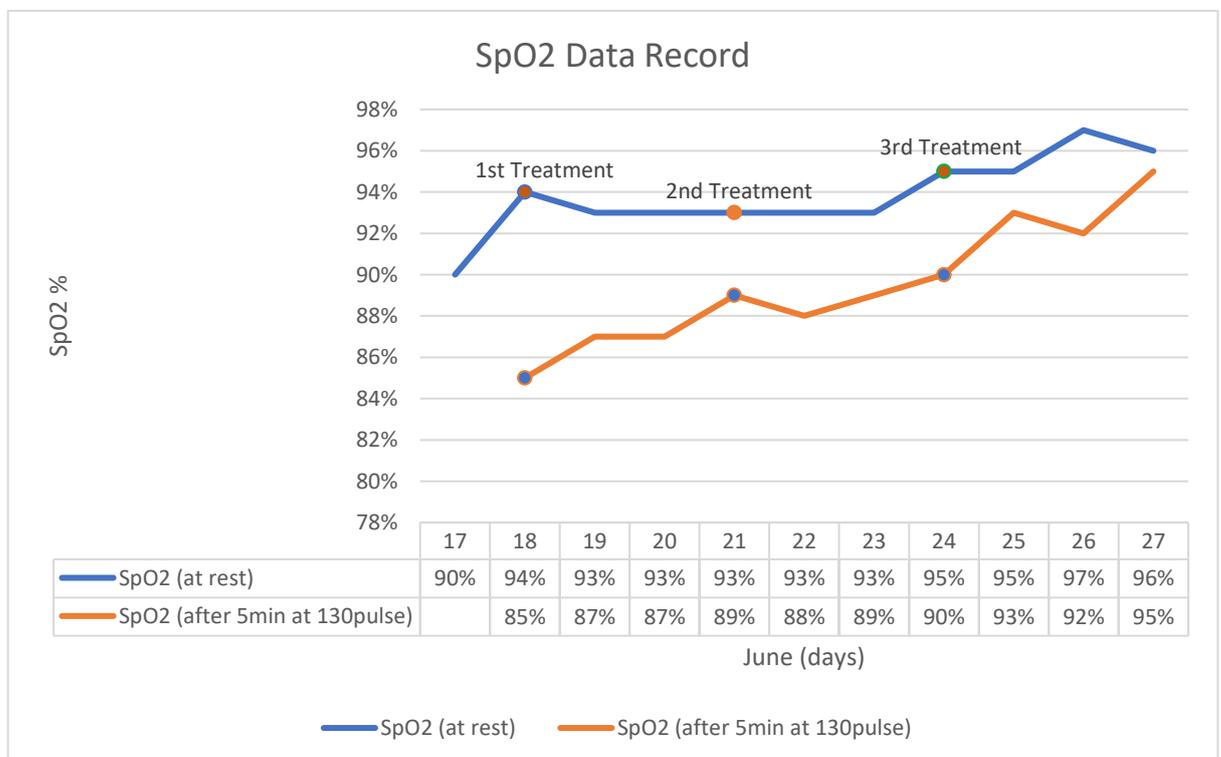


Figure 3. SpO2 changes at rest and at 130 bps of pat. 18

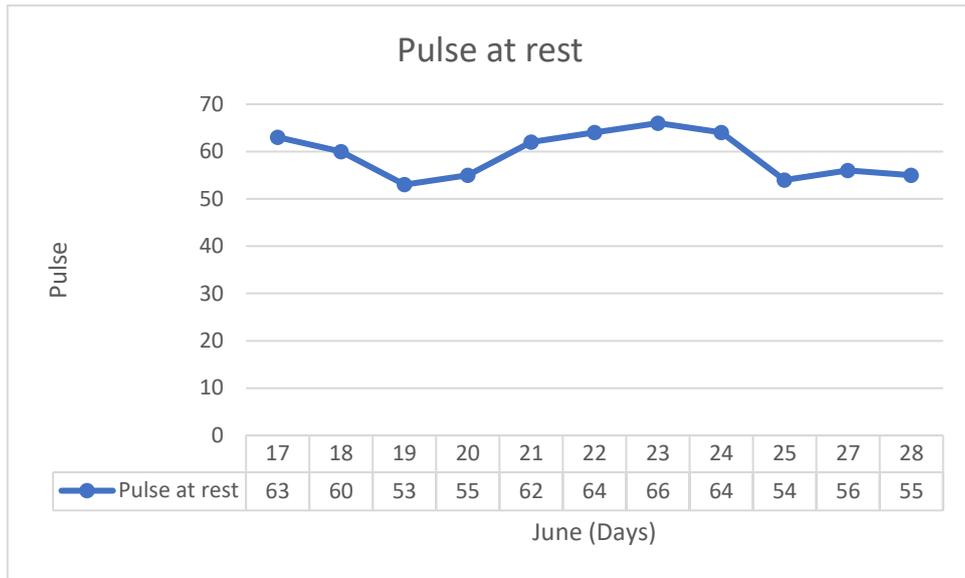


Figure 4. Pulse monitoring at rest