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COVID-19: a killer with »silent hypoxemia«

Covid-19: ubijalec s »tiho hipoksemijo«

Matevž Harlander,[1,2] Janez Tomažič,[2,3] Matjaž Turel,[1] Matjaž Jereb[2,3]

[1] Department of Pulmonary Diseases and Allergy, Division of Internal Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia
[2] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[3] Department of Infectious Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia

Correspondence/ Korespondenca:
Matevž Harlander, e: matevz.harlander@gmail.com

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Abstract

The most frequent symptoms and signs of SARS-CoV-2 infection are fever, cough, fatigue and weakness, loss of smell and taste and headache. In some COVID-19 patients, there is rapidly progressing hypoxemia which is not accompanied by dyspnea or perception of increased work of breathing. It is called “silent hypoxemia” and it can be life-threatening. We present two cases of patients with COVID-19 pneumonia, silent hypoxemia, and rapidly progressing respiratory failure. Possible pathophysiological mechanisms are discussed.

Izvleček

Najpogostejši simptomi in znaki okužbe z virusom SARS-CoV-2 so vročina, kašelj, slabo počutje s hudo splošno oslabelostjo, izguba vonja in okusa ter glavobol. Pri nekaterih bolnikih s pljučnico pri covidu-19 opažamo hitro poglabljajočo se hipoksemijo, ki je ne spremlja občutek pomanjkanja zraka oziroma dušenja. Bolnik ne čuti povečanega dihalnega dela. Imenujemo jo »tiha hipoksemija« in je lahko življenje ogrožajoča. Predstavljamo primera dveh bolnikov s pljučnico, povezano s covidom-19, tiho hipoksemijo in hitro napredujočim dihalnim popuščanjem ter razpravljamo o možnih patofizioloških vzrokih.

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1 Introduction

The agent of the novel coronavirus infectious disease (COVID-19) is the novel coronavirus SARS-CoV-2. The disease very quickly caused global public health emergency conditions due to the lack of herd immunity and fast virus transmission. The most frequent symptoms and signs of infection with the SARS-CoV-2 virus are fever, cough, general malaise and fatigue, loss of smell and taste and headache (1). The infection can proceed without any symptoms, with a mild to severe symptoms and a very severe course, which can result in the patient’s death. With more severe types of the disease, the lungs are most frequently affected. Radiographs and CTs of lungs show fairly characteristic bilateral areas of ground-glass opacities, inter- and interlobular septal thickening, and areas of alveolar thickening. The changes are most often distributed peripherally but may also be diffuse. If ARDS does not develop, they reach their maximum between the 7th and the 14th

day after the onset of symptoms (2,3). In some patients with COVID-19 pneumonia, a fast-exacerbating hypoxaemia can be noticed, which is not accompanied by a feeling of shortness of breath (dyspnoea). The patient does not appear to have increased breathing effort. It is also called "silent hypoxaemia". With no clear clinical indications, except for increased breathing frequency, a severe hypoxemic respiratory failure develops. It results in insufficient oxygen supply of organs and tissues, impairing their function. "Silent hypoxaemia" can be a fatal problem for patients in home care, as their vital signs are not monitored. This article presents two cases of patients with COVID-19 pneumonia, silent hypoxaemia and rapid progression respiratory failure, and discusses possible pathophysiological mechanisms of such clinical picture.

2 Case report

2.1 Patient 1 case report

A 48-old man fell ill three days before being admitted to the Department of Infectious Diseases (DID) of the University Medical Centre Ljubljana (UMC Ljubljana) with a fever of 38.5° C, muscle pain, headache, and occasional dry cough. The patient was obese and was treated for type 2 diabetes. Fourteen days before being admitted, he was in contact with a work colleague with proven COVID-19. At the emergency outpatient clinic, they measured 85% haemoglobin oxygen saturation ($sHbO_2$), using a pulse oximeter while he was supplied oxygen through the 100% O_2 non-rebreathable mask. Because of persistent hypoxaemia in spite of oxygen therapy, he was admitted directly into the Intensive Care Unit (ICU) of DID, UMC Ljubljana, where they measured only 60% $sHbO_2$. The patient's respiratory rate was 42/min, his blood pressure was 163/60 mmHg, his pulse 127/min, body temperature 37.5° C, and his skin was cold and wet. The arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO_2 / FiO_2) was 93. The ultrasound showed bilateral B-lines above the lungs. Orientation ultrasound of the heart did not show any abnormalities. In spite of severe hypoxaemia, the patient was awake, cooperating, made sensible conversation, was calm and did not have a significant feeling of suffocation. The patient's general condition and absence of dyspnoea were disproportionate with the results of the measurements of his vital functions. We planned mechanical ventilation, however, the patient wanted to conduct a telephone call first. After preparation, we then intubated the patient and connected him to the mechanical ventilation system. Among the laboratory results of his blood tests, the following increased values stood out (normal values provided in brackets): C-reactive protein (CRP) 293 mg/L (below 5 mg/L), leukocyte concentration 16.7 x 10^9/L (4.0 – 10.0 x 10^9/L), glucose 15.2 mmol/L (3.6 – 6.1 mmol/L), urea 13.2 mmol/L (2.8 – 7.5 mmol/L), creatinine 188 µmol/L (44 – 97 µmol/L), D-dimer 1296 µg/L (below 500 µg/L), fibrinogen 4.1 g/L (1.8 – 3.5 g/L), interleukin 6 (IL-6) 199 ng/L (below 7.0 ng/L), lactate dehydrogenase (LDH) 17.10 µkat/L (below 4.13 µkat/L), creatine kinase (CK) 8.7 µkat/L (below 2.85 µkat/L), myoglobin 258.6 µg/L (below 110 µg/L), troponin 351 ng/L (below 58 ng/L) and NT-proBNP 5762 ng/L (below 125 ng/L). The lymphocyte concentration was low, while the thrombocyte and procalcitonin concentrations were within normal values. The X-ray of the lungs showed extensive bilateral interstitial-alveolar consolidations, which, given their distribution, are typical for COVID-19 pneumonia (Figure 1). The swab of the nasopharyngeal space was positive for the SARS-CoV-2 virus. The results of microbiological examinations (haemoculture, urine culture and endotracheal aspirate) were negative. Because of a suspected secondary bacterial pneumonia, he received a broad-spectrum antibiotic. For treating the SARS-CoV-2 infection, he received lopinavir with ri-

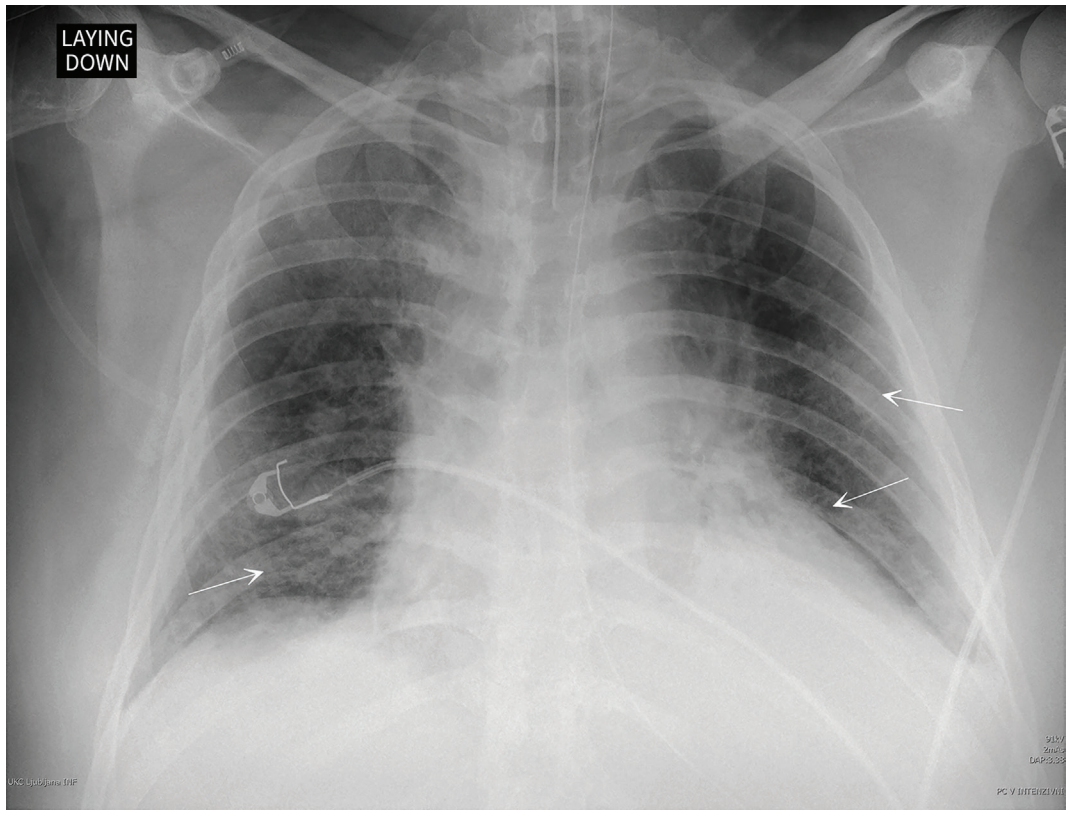

Figure 1: Radiogram of the lungs of patient 1 showed extensive bilateral cases of interstitial-alveolar thickening.

tonavir and chloroquine. After 28 days of mechanical ventilation, the patient was extubated and transfered to the ward.

2.2 Patient 2 case report

A 50-year-old man with a confirmed infection with the SARS-CoV-2 virus without comorbidities was admitted to DID UMC Ljubljana because he was unable to self-isolate. The epidemiological history was negative. He fell ill the day before being admitted with a fever of 39.7°C and with a moderate headache. At admittance, he did not have a fever, was not affected and was haemodynamically stable. He did not require supplemental oxygen. Laboratory results showed moderately increased CRP, lymphopenia and thrombocytopenia. The results of other biochemical blood examinations and blood pictures were within normal values. The X-ray of his lungs showed the presence of interstitial-alveolar consolidations in the right upper lobe (Figure 2). Over the next few days, his body temperature persisted above 38°C, with an occasional dry cough and with liquid bowel movements several times a day. On the fifth day, the patient's condition exacerbated. Respiratory rate was over 25/min. $sHbO_2$ measured with a pulse oximeter was 86%. Arterial blood gas test showed pO_2 value of 6.6 kPa. In order to keep $sHbO_2$ above 94%, he required supplemental oxygen with more than 35% via a Venturi mask (VM). The patient stated he felt good, did not feel short of breath, or had any pain in the chest. The need for oxygen increased over the next four hours. When the need to oxygen suplementation rose above 60% via VM, the patient was moved to the ICU. He was unaffected, had a respiratory rate of 19/min, while the $sHbO_2$ measured with a pulse oximeter was at 97%, with blood pressure of 152/80 mmHg, pulse of 93/min and body tem-

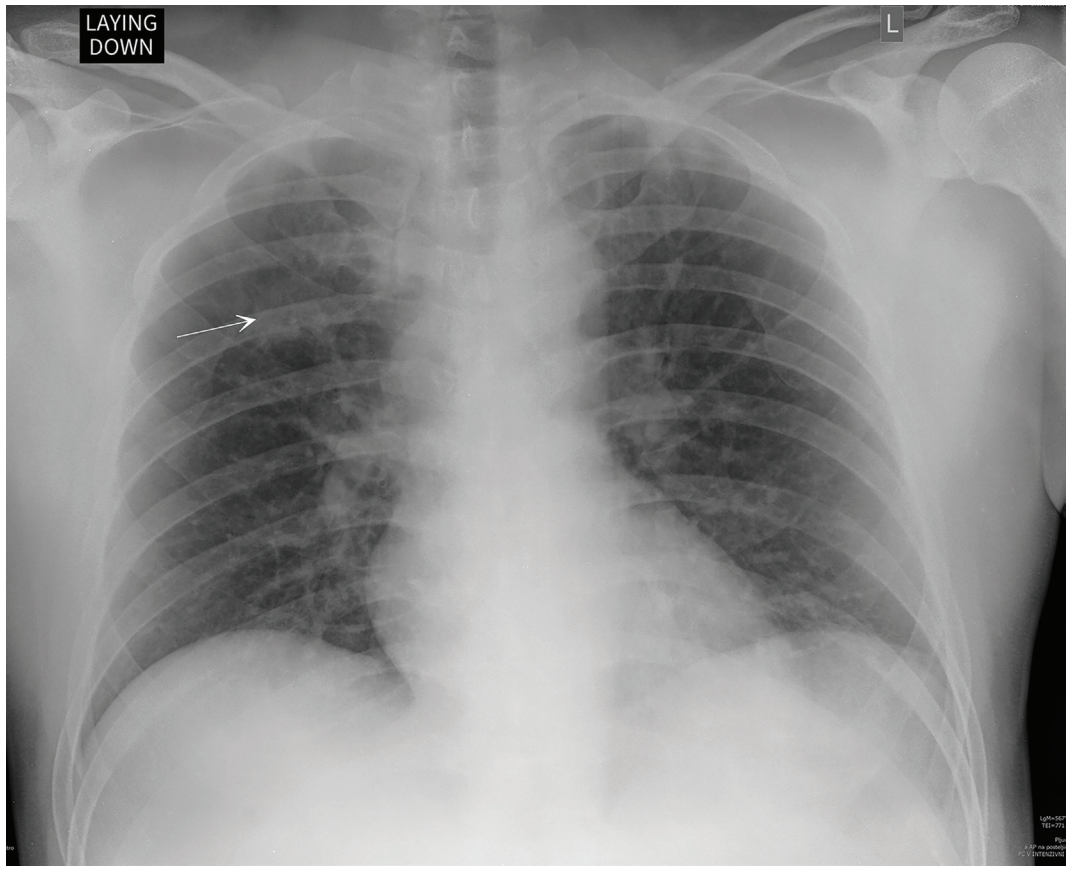

Figure 2: Radiogram of the lungs of patient 2 showed the presence of thickening in the right upper lobe.

perature of 37.4°C. The PaO_2 / FiO_2 ratio was at 132. Among the laboratory results, the following increased values stood out: CRP 189 mg/L (below 5 mg/L), glucose 6.6 mmol/L (3.6 – 6.1 mmol/L), Aspartate transaminase (AST) 1.73 µkat/L (below 0.58 µkat/L), Alanine transaminase (ALT) 1.93 µkat/L (below 0,77 µkat/L), gamma-glutamyl transferase (gamma-GT) 2.49 µkat/L (below 0.92 µkat/L), D-dimer 742 µg/L (below 500 µg/L), fibrinogen 8.3 g/L (1.8 – 3.5 g/L), IL-6 56.6 ng/L (below 7.0 ng/L), LDH 8.02 µkat/L (below 4.13 µkat/L), CK 17.74 µkat/L (below 2.85 µkat/L) and myoglobin 184.3 µg/L (below 110 µg/L). The lymphocyte concentration was low, while the leukocyte, thrombocyte and procalcitonin concentrations were within normal values. The control X-ray of the lungs showed an exacerbation. The areas of consolidations in the upper half of the right lung were more extensive and there were new consolidations bilaterally (Figure 3). The ultrasound examination showed only a few B-lines right above the lungs. Orientation ultrasound of the heart did not show any abnormalities. After being admitted to the ICU, the patient's condition additionally exacerbated. His respiratory rate was over 35/min, and his need for oxygen increased. When oxygen was supplied through the 100% non-rebreathable mask, the arterial blood gas test measured partial oxygen pressure of 7.1 kPa. During this time, the patient was awake, cooperating, made sensible conversation, was calm and did not have any feeling of suffocation. After preparation, we then intubated the patient and connected him to the mechanical ventilation system. For treating the SARS-CoV-2 infection, he received lopinavir with ritonavir and chlo-

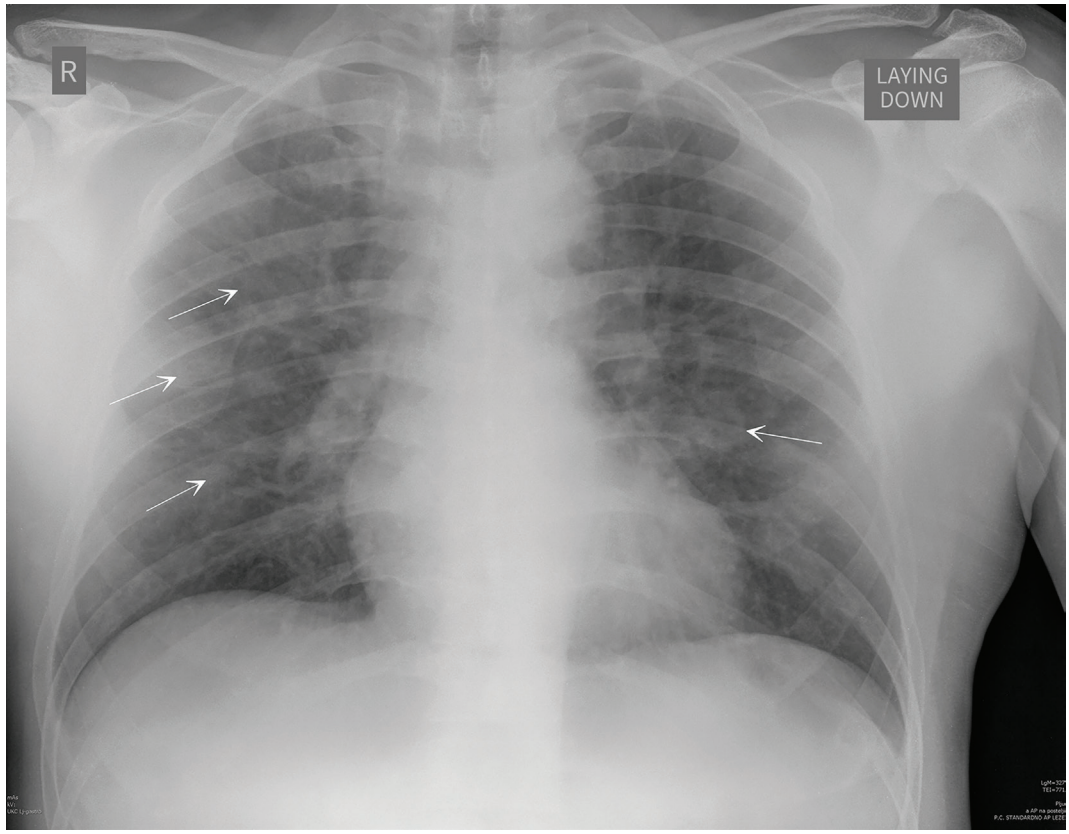

Figure 3: Control image of patient 2's lungs after an exacerbation. Thickening in the right upper lobe is more extensive, additional changes are visible bilaterally.

roquine. With additional increase of laboratory indicators of inflammation and the isolation of the bacteria Pseudomonas aeruginosa from the endotracheal lavage, he received a broad-spectrum antibiotic because of suspected hospital pneumonia. After nine days of mechanical ventilation, the patient was extubated and moved to the ward. He was released from the hospital after 24 days of treatment, mobile, with no objective consequences and subjective problems.

3 Discussion

SARS-CoV-2 can result in a severe form of pneumonia that requires treatment with mechanical ventilation or even with extracorporeal membrane oxygenation (ECMO) (4). The patients who stand out are those with COVID-19 who – in spite of severe hypoxaemia and extensive changes in imaging examinations of the lungs – do not have any feeling of dyspnoea, even if this is expected from experience in treating other pneumonias. The proportion of such cases is not known. The pathophysiology of this condition is also not completely clear.

Dyspnoea is a subjective feeling of uneasiness when breathing and frequently accompanies acute and chronic diseases (5). The main source of information on the "need to breath" are the central and peripheral chemoreceptors and the vagal C-fibres in the lungs. Mechanoreceptors in the chest cavity and the stretch receptors in the lungs also participate. It appears that dyspnoea occurs when an afferent impulse is not followed by a sufficient (expected) increase in ventilation, either because of a failure of the respiratory pump or a lung disease (6). Hypoxaemia stimulates increased minute ventilation

through chemoreceptors; however, it does not cause dyspnoea. In experiments on healthy volunteers, hypoxaemia did not significantly increase the felling of dyspnoea, even when pO_2 was reduced to 5.3 kPa (which corresponds to 75% $sHbO_2$), if they were able to increase minute ventilation (7). There are significant differences between individuals in the perception of dyspnoea with regard to objective impulses (8).

"Silent hypoxaemia" in COVID-19 pneumonia is most likely the result of the onset of right-to-left shunts and ineffective hypoxic vasoconstriction with a relatively well-retained lung compliance and with retained physiological dead space. In right-to-left sunts blood moves from venous system into arterial circulation, without oxygenating in the lungs. SARS-CoV-2 enters the cells through a type 2 angiotensin-converting enzyme (ACE2), found on the cellular membrane (9). In the lungs it is especially prevalent on type 2 pneumocytes, which among other things produce surfactant, which lowers the surface tension, making it possible for the alveoli to remain open. After the infection, there is an inflammation and a decay of type 2 pneumocytes, which leads to a collapse of alveoli and atelectasis, which are unequally distributed across both lungs. Right-to-left shunts occur in atelectasis, causing hypoxaemia. Hypoxic vasoconstriction is a physiological mechanism in the lungs, in which a vasoconstriction of pulmonary arterioles occurs in the parts of the lungs with poor ventilation (and consequently low partial oxygen pressure in the alveoli). This way, the lungs reduce right-to-left shunts and improve oxygenation (sometimes at the cost of increased pressures in the right ventricle). There are significant differences between individuals in the effectiveness of hypoxic vasoconstriction (10). In COVID-19 pneumonia, the effect on the lungs is diffuse and uneven, and therefore hypoxic vasoconstriction can be an important mechanism for sustaining oxygenation. People with a poorer response may develop a more severe hypoxaemia. The ACE2 enzyme could also be involved in the pathophysiology of hypoxic vasoconstriction failure. ACE2 reduces hypoxic vasoconstriction and functions as a vasodilator of lung arteries (11). It is paradoxical that in SARS-CoV-2 virus infection, there can be a local reduction in the ACE2 activity (12). In a recent short report, authors from Italy found that patients with hypoxaemia and a retained lung compliance have a detectable hyperperfusion of the unventilated parts of their lungs visible on a computed tomography (CT) image (13), confirming the hypothesis of ineffective hypoxic vasoconstriction. Similarly, unexpected abnormalities in the perfusion of affected lungs that may indicate a failure of regulation mechanisms, were also described in a series of cases from the USA (14).

Another characteristic of COVID-19 patients with "silent hypoxaemia" is retained lung compliance. In this phase of the disease, there is not much consolidated/unventilated tissue, which allows the patient to achieve satisfactory tidal volume (13).

One of the possible causes of hypoxaemia in COVID-19 pneumonia are pulmonary embolisms and the onset of microthromboses in the pulmonary vasculature, which has been recorded in severe forms of the disease (15). Considering the current data, this is most likely not the reason for the clinical picture of "silent hypoxaemia", as increased physiological dead space would result in dyspnoea.

COVID-19 pneumonia therefore causes hypoxaemia, which automatically increases ventilation (faster and deeper respiration) (10). However, with increased breathing, a patient achieves satisfactory minute ventilation, so they do not have the feeling of dyspnoea. Increased minute ventilation results in hypocapnia. Hypocapnic hypoxaemia affects the cognitive function and may cause the feeling of well-being (so the alternative term "happy hypoxaemia" is sometimes used) (16).

Consequently, we may identify the condition as critical with delay.

In "silent hypoxaemia", the patient's health is unchanged for a while, then it may improve or exacerbate. The exacerbation may occur because of advancing COVID-19 pneumonia or because of intensive breathing, which creates negative intrapleural pressure, which may result in an interstitial oedema (13). Lung compliance suddenly declines and a classic acute respiratory distress syndrome (ARDS) can be seen. The patient's condition significantly exacerbates, and he must be taken into a hospital, frequently requiring intubation and mechanical ventilation. Because of falls during hypoxaemia, patients may even end up in trauma care units. It is interesting that one of the studies recognised dyspnoea as an independent prognostic factor of a poor outcome of COVID-19 pneumonia (17). Patients with no dyspnoea had perhaps retained a better lung compliance or slower advancement into the interstitial oedema and ARDS.

We have to be especially careful of potential development of hypoxaemia in vulnerable people, where the course of the disease can be severe (> 60 years of age, chronic comorbidities, immune disorders) (18); but due to the apparent mild course of the disease, there is no need for hospitalisation at the time of diagnosis. During the first 14 days, it is recommended to monitor the basic vital functions with a pulse oximeter, with the measurements conducted by either the patients themselves or their personal/retirement home physicians. A second modern option is to use systems for data transfer from the home to the healthcare centre using telemetry. The values measured at home are transmitted to a monitoring centre from home over a data connection, where a medically qualified person assesses them critically and responds appropriately, when needed.

4 Conclusion

A COVID-19 pneumonia may be accompanied by "silent hypoxaemia", and therefore we must carefully monitor oxygenation of COVID-19 patients. It is a potential cause of death of patients who die of this new infectious disease in a home environment that is not medically monitored.

Both patients agreed with the publication of the article, describing their cases.

References

1. Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, et al. Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. J Med Virol. 2020;92(10):1902-14. DOI: 10.1002/jmv.25884 DOI: 32293716
2. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology. 2020;295(3):715-21. DOI: 10.1148/radiol.2020200370 DOI: 32053470
3. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20(4):425-34. DOI: 10.1016/S1473-3099(20)30086-4 DOI: 32105637
4. Hong X, Xiong J, Feng Z, Shi Y. Extracorporeal membrane oxygenation (ECMO): does it have a role in the treatment of severe COVID-19? Int J Infect Dis. 2020;94:78-80. DOI: 10.1016/j.ijid.2020.03.058 DOI: 32251794
5. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al.; American Thoracic Society Committee on Dyspnea. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 2012;185(4):435-52. DOI: 10.1164/rccm.201111-2042ST DOI: 22336677
6. Burki NK, Lee LY. Mechanisms of dyspnea. Chest. 2010;138(5):1196-201. DOI: 10.1378/chest.10-0534 DOI: 21051395

7. Moosavi SH, Golestanian E, Binks AP, Lansing RW, Brown R, Banzett RB. Hypoxic and hypercapnic drives to breathe generate equivalent levels of air hunger in humans. J Appl Physiol (1985). 2003;94(1):141-54. DOI: 10.1152/japplphysiol.00594.2002 DOI: 12391041
8. Adams L, Chronos N, Lane R, Guz A. The measurement of breathlessness induced in normal subjects: individual differences. Clin Sci (Lond). 1986;70(2):131-40. DOI: 10.1042/cs0700131 DOI: 3956105
9. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215:108427. DOI: 10.1016/j.clim.2020.108427 DOI: 32325252
10. Weil JV, Byrne-Quinn E, Sodal IE, Friesen WO, Underhill B, Filley GF, et al. Hypoxic ventilatory drive in normal man. J Clin Invest. 1970;49(6):1061-72. DOI: 10.1172/JCI106322 DOI: 5422012
11. Veit F, Weissmann N. Angiotensin-converting enzyme 2 activation for treatment of pulmonary hypertension. Am J Respir Crit Care Med. 2013;187(6):569-71. DOI: 10.1164/rccm.201301-0133ED DOI: 23504361
12. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med. 2020;76:14-20. DOI: 10.1016/j.ejim.2020.04.037 DOI: 32336612
13. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020;201(10):1299-300. DOI: 10.1164/rccm.202003-0817LE DOI: 32228035
14. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis. 2020;S1473-3099(20):30367-4. DOI: 10.1016/S1473-3099(20)30367-4 DOI: 32359410
15. Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series. J Thromb Haemost. 2020;18(7):1752-5. DOI: 10.1111/jth.14828 DOI: 32267998
16. Ottestad W, Søvik S. COVID-19 patients with respiratory failure: what can we learn from aviation medicine? Br J Anaesth. 2020;125(3):e280-1. DOI: 10.1016/j.bja.2020.04.012 DOI: 32362340
17. Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, et al. Association Between Hypoxemia and Mortality in Patients With COVID-19. Mayo Clin Proc. 2020;95(6):1138-47. DOI: 10.1016/j.mayocp.2020.04.006 DOI: 32376101
18. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;81(2):e16-25. DOI: 10.1016/j.jinf.2020.04.021 DOI: 32335169