Pulmonary edema in covid-19 diseased patients and patients with high altitude pulmonary edema (hape) – are there similarities in pathophysiology, treatment and respiratory rehabilitation?

Assist. prof. dr. JURIJ GORJANC, MD, PhD
Hospital of St. John of God, Spitalgasse 26, 9300 St. Veit/Glan, Austria
e-mail: jurij.gorjanc@mf.uni-lj.si

Abstract

Introduction: Patients with pulmonary edema in COVID-19 and patients with high altitude pulmonary edema (HAPE) have many similarities in their history, clinical examination and CT-scans. It is unclear, whether pathophysiologic ways and management are similar despite different etiology and what are the differences in respiratory rehabilitation of both groups. Methods: Literature overview and analysis of data from renowned textbooks on mountain medicine and Pubmed publications on COVID-19 have been performed. Results: The reason of pulmonary edema in COVID-19 is in greater permeability of the alveolocapilary membrane. This is due to cytokine (inflammatory) response to virus SaRS-CoV-2 infection. Pulmonary edema in HAPE however, develops as a consequence of acute hypertension in pulmonary artery, which is a consequence of hypoxic pulmonary vasoconstriction due to hypobaric hypoxia at high altitude. In HAPE the drugs can turn the patients` lung function to normal within hours/days. In COVID-19, the lung function improves very slowly within weeks/months. Conclusions: According to analysis of published papers, there is no relevant data about pathophysiological similarities of pulmonary edema in HAPE and COVID-19. On the contrary, in HAPE hypoxia is the cause and in COVID-19 hypoxia is the consequence. In the times of COVID-19 pandemic, the possible COVID-19-etiology of pulmonary edema in high altitudes should be considered and excluded. Pulmonary rehabilitation in patients after HAPE is fast and not needed on long term. Pulmonary rehabilitation in COVID-19 survivors takes much more time, but improves respiratory function. Key words: High altitude pulmonary edema, COVID-19, SaRS-CoV-2, respiratory physiotherapy.

Pljučni edem pri boleznih kovid-19 bolesnikih in bolnikih z visoko nadmornimi pulmonarnim edemom (hape) – ali obstojajo podobnost v patofiziologiji, zdravljenju in rehabilitaciji dihal?

Povzetek

Uvod: Pljučni edem (HAPE) ima veliko podobnosti v svoji zgodovini, kliničnem pregledu in CT-preiskavah. Ni jasno, ali so si patofiziološki načini in zdravljenje podobni kljub različni etiologiji in kakšne so razlike v rehabilitaciji dihal obeh skupin. Metode: Opravljen je bil pregled literature in analiza podatkov iz priznanih učbenikov gorske medicine in objavljenih publikacij o COVID-19. Rezultati: Razlog za pljučni edem pri COVID-19 je v večji prepustnosti alveolokapilarne membrane. To je posledica citokinskega (vnetnega) odziva na okužbo z virusom SaRS-CoV-2. Pljučni edem pri HAPE pa se razvije kot posledica akutne hipertenzije v pljučni arteriji, ki je posledica hipoksične pljučne vazokonstrikcije zaradi hipobarične hipoksije na visoki nadmorski višini. Zdravila HAPE lahko v urah / dneh normalizirajo delovanje pljuč pri bolnikih. Pri zdravilu COVID-19 se pljučna funkcija v tednih / mesecih zelo počasi izboljšuje. Zaključki: Glede na analizo objavljenih člankov ni ustreznih podatkov o patofizioloških podobnostih pljučnega edema pri HAPE in COVID-19. Nasprotno, pri HAPE je vzrok hipoksija, pri COVID-19 pa hipoksija. V času pandemije COVID-19 je treba preučiti in izključiti morebitno etiologijo pljučnega edema v velikih nadmorskih višinah. Pljučna rehabilitacija pri bolnikih po HAPE je hitra in dolgoročno ni potrebna. Pljučna rehabilitacija pri preživelih s COVID-19 traja veliko več časa, vendar izboljša dihalno funkcijo. Ključne besede: pljučni edem na visoki nadmorski višini, COVID-19, SaRS-CoV-2, dihalna fizioterapija

1. INTRODUCTION

Since the COVID-19 pandemic has emerged in december 2019, the Sars-CoV2 virus became a cause of a new life-threatening disease. By the end of 2020, almost two million people died globally due to this infection and its complications and consequences (1). New diseases, especially life-threatening illnesses like COVID-19, may provoke new ideas for its management in order to help critically ill patients (2). Speculations additionally prosper due to numerous poorly relevant information from different reports and widespread social media (3, 4). To date, no specific causal therapy has been found for COVID-19, except some general antiviral drugs that help to reduce the virus load. Pulmonary edema is a potentially lethal condition in many diseases, including COVID-19 (5). One of the "logical" ideas could be using medications, efficient in pulmonary edema of other causes, in COVID-19 patients with pulmonary edema (6).

High altitude pulmonary edema (HAPE), as defined today, is a critical form of high-altitude sickness (7). When recognized too late and not treated with proper medication, it can lead to death (8, 9). Some authors found parallels between HAPE and pulmonary edema in COVID-19 (10). Touting such an approach, as good as it might appear, it should be observed with utmost criticism (11). Luckily, many researchers are warning of simplified solutions without thorough scientific research and relevance of clinical data (11, 12).

Respiratory rehabilitation after HAPE, that is properly treated, is usually fast and mostly spontaneous unless other co-morbidities are present (13). Respiratory physiotherapy in COVID-19 is probably needed to achieve respiratory improvement.

2. METHODS

In order to answer the question from the title, literature review of mountain medicine textbooks and PubMed database on COVID-19 pulmonary edema, HAPE and respiratory rehabilitation have been perfomed (72 hits).

3. RESULTS

Auerbach`s Textbook of Wilderness Medicine defines HAPE as a direct effect of elevated pulmonary artery pressure (PAP). Without high PAP, no HAPE diagnosis can be made (8). Elevated PAP is an organism response to hypobaric hypoxia and hypoxic vasoconstriction. Elevated plasma fluid permeability of the alveolocapilary membrane is observed, probably as a consequence of relative inactivity of sodium channels. This phenomenon is most distinctly described in individuals, who are more susceptible for HAPE (8). Last edition of West`s Textbook "High altitude medicine and Physiology" supports the thesis that every individual can suffer HAPE, but climbers with relative pulmonary hypertension get it more frequently and in more severe form (14). According to some data, climbers with HAPE-history, children and younger adults could be among them (15). The question, if HAPE susceptibility has a genetic predisposition, could be answered after report of nitric oxyde (NO) metabolism impairment (with PAP elevation) has been published (16). Official Handbook of the Swiss Alpine Club (SAC) citates same research, where higher alveolocapilary membrane permeability in HAPE is the direct effect of elevated PAP. A vicious circle cascade follows, which only can be stopped with descent to lower altitude, oxygen administration and proper medication (17).

Main steps in the HAPE cascade are listed in Table 1.

Main cause	HIGH-ALTITUDE (HYPOBARIC) HYPOXIA
Pathogenesis	1. Extreme hypoxic pulmonary vasoconstriction and elevated PAP (acute pulmonary hypertension). The phenomenon is not diffuse over the lung, but areas with greater vasonconstriction are described, leading to "patchy" pattern on lung x-ray.
	2. Elevated capillary pressure (pulmonary capillary hypertension).
	3. Pressure-induced elevated permeability of sodium channels in the alevolo-capilary membrane ("stress failure").
	4. Slower resorbtion and excretion of alveolar fluid from the alveoli.

Table 1 – Factors for the development of HAPE

Pulmonary edema in COVID-19 is likewise triggered by elevated permeability of the alveolocapilary membrane. But this high permeability in COVID-19 is, unlike HAPE, an effect of cytokine reaction to virus infection. Hypoxia in COVID-19 is a consequence and not the cause (18). Inflammation is the main cause that effects in the destruction of surfactant and in the imbalance of ventilation/perfusion ratio (3, 4, 18, 20).
Some authors report, that there are similarities between HAPE and COVID-19 pulmonary edema. Both diseases, in its heaviest form, result in micro- and macrothrombi, that can additionally elevate the pressure in the pulmonary capillaries and result in higher permeability (2, 21). Other reports showed that pulmonary edema in COVID-19 might be an effect of impaired function of calcium channels (22).
Summary of principal steps in the COVID-19 pulmonary edema cascade is listed in Table 2.

Main cause	VIRUS INFECTION AND INFLAMMATION
Pathogenesis	1. Type 2-alveolar cells release inflammatory signals.
	2. Activation of macrofages.
	3. Release of cytokines and susequent vasodilatation; cell-packing within the alveolocapilary membrane, possibly formation of microthrombi.
	4. Fluid accumulation within alveoli.
	5. Surfactant dilution and additionally higher membrane permeability results in more edema (vicious circle).

Table 2 – Main factors for the development of COVID-19 pulmonary edema

6. DISCUSSION

HAPE appears as exacerbation of Acute Mountain Sickness, when climbers ascend too quickly to altitudes above 3000 meters. Hypoxia triggers a pathophysiologic cascade, which results in pulmonary edema. This edema is hydrostatic and non-cardiac, non-inflammatory (7). Hypobaric hypoxia triggers hypoxaemia and after manifestation of HAPE the hypoxaemia worsens. The main mechanism is hypoxic vasoconstriction, which can elevate systolic PAP from normal (18-25mmHg) to as high as 80-100 mmHg (23). A combination of descent, Gamow bag, drugs and oxygen given to a patient normally improve his condition rapidly and many patients are soon able to go to high altitude again, with some precautions

concerning acclimatization (8, 9, 19, 24). An inflammatory component can exacerbate the initial clinical situation in HAPE, but this is rare and does not play a crucial role in the HAPE pathophysiology (24). Unless treated appropriately as described above, mortality rate in HAPE is high (8, 9). It can be at 11%, when treated appropriately and as high as 50%, when untreated (25). That's why climbers remind of an old saying which defines "any respiratory illness at high altitude as mountain sickness (and/or HAPE), until we the opposite can be proven" (8, 9). Accordingly, to this proverb, in recent years, many cases of whooping cough on Mt. Kilimanjaro have been falsely treated with drugs for acute mountain sickness (13).

In COVID-19, on the other side, pneumonia develops on day 5 or later after beginning of the symptoms. Pneumonia with its exacerbations is one of the main causes of death in this disease, especially in acute respiratory distress syndrom (ARDS), including inflammatory pulmonary edema (26). ARDS is present in 60-70% of patients with complications after COVID-19 pneumonia (27). Inflammatory reactions are thus the main cause for the pathophysiological cascade in COVID-19 and hypoxaemia is a result, not the trigger (18). Another important difference in COVID-19 pneumonia towards HAPE is impairment of other organs or organ systems like heart (cardiomyopathy), kidneys (nephropathy), coagulation balance and even central nervous system (28, 29); a phenomenon, which is not present in HAPE. Additionally, the course of COVID-19 disease is of prolonged duration, including weeks or even months of mechanical ventilation. Mortality rate in COVID-19 with pneumonia and its exacerbations is as high as 25% (6). While oxygen is one of the causal therapies in HAPE, it does not help to remove the cause of the disease in COVID-19. It can improve the hypoxaemia, but not the lung injury (30). Vasodilatative medication, used to improve the symptoms in HAPE, has no impact on COVID-19 pulmonary edema. Vasodilative drugs (nifedipine, sildenafil) can be even harmful, when used in COVID-19 (30, 31). Although HAPE and COVID-19 are triggered by different mechanisms, differential diagnosis of both diseases is important, especially in the time of pandemic. It is possible, especially in middle- and high-altitude villages to diagnose COVID-19 at high altitude (30).

Respiratory rehabilitation after HAPE is usually short. HAPE patients are predominantly young males, exposed to hypobaric hypoxia at high altitude and without concomitant respiratory diseases (7, 8, 15, 32). Once they descend or are transported to lower altitude and treated with additional oxygen and medication, the symptoms improve or even dissapear. There are reports of alpinists summiting eight-thousenders immediately after suffering HAPE on the same Himalayan expedition (32, 33).

On the other hand, according to recent reports, respiratory physiotherapy plays a crucial role in the rehabilitation of these patients. COVID-19 patients with serious respiratory distress syndrome need prolonged respiratory support, physiotherapy and physical activity in order to achieve satisfactory respiratory function (34, 35, 36). Intensive respiratory physiotherapy in COVID-19 patients significantly improves their breathing status (37).

7. CONCLUSIONS

There is no evidence, that COVID-19 pneumonia and HAPE have similar pathophysiologic trigger mechanisms. In contrary, in HAPE, hypoxia is the cause and not only the consequence of the disease, as is the case in COVID-19. The main cause of COVID-19 is virus infection and inflammation reaction of the organism.

Medication for HAPE is not only ineffective in COVID-19 patients, but can be potentially dangerous. However, it is not unprobable in the near future, to meet COVID-19 patients at middle and high altitudes. Respiratory rehabilitation should be well planned, organized and performed in COVID-19 patients as it can importantly improve their respiratory capacity.

8. REFERENCES

1. *University John Hopkins, Baltimore (2020). An interactive web-based dashboard to track COVID-19 in real time. https://systems.jhu.edu/research/public-health/ncov/.*
2. *Anoop UR,Verma K. Pulmonary Edema in COVID19-A Neural Hypothesis. ACS Chem Neurosci . 2020 Jul 15;11(14):2048-2050.*
3. *Ghelichkhani P, Esmaeili M. Prone Position in Management of COVID-19 Patients; a Commentary. Arch Acad Emerg Med. 2020 11;8(1):e48.*
4. *Bahloul M, Ketata W, Lahyeni D, Mayoufi H, Kotti A, Smaoui F , Kallel N, Daoud E , Bouaziz M, Kammoun S. Pulmonary capillary leak syndrome following COVID-19 virus infection. J Med Virol 2020 10;10.1002/jmv.26152. Online ahead of print.*
5. *Cavezzi A, Troiani E , Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clin Pract 2020 28;10(2):1271.*
6. *Li J, He X, Yuan Y et al. Meta-analysis investigating the relationship between clinical features, outcomes, and severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia. Am J Infect Control. 2020.12;30369-2.*
7. *Maggiorini M, Melot C, Pierre S et al. High altitude pulmonary edema is initially caused by an increase in capillary pressure. Circulation 2001; 103: 2078-83.*
8. *Hackett PH, Roach RC: High-Altitude Medicine. In: Auerbach PS (ed): Wilderness Medicine, 6th edition; Elsevier, Mosby, St. Louis, MO 2012: 1-26.*
9. *Harris NS. Chapter 136. High-altitude medicine. In: Walls RM, Hockberger RS, Gausche-Hill M. Rosen's Emergency Medicine: Concepts and Clinical Practice. 9th ed. Philadelphia: Elsevier; 2018: 1787.*
10. *Solaimanzadeh I. Acetazolamide, Nifedipine and Phosphodiesterase Inhibitors: Rationale for Their Utilization as Adjunctive Countermeasures in the Treatment of Coronavirus Disease 2019 (COVID-19). Cureus 2020 20;12(3):e7343.*
11. *Luks AM, Swenson ER. COVID-19 Lung Injury and High Altitude Pulmonary Edema: A False Equation with Dangerous Implications. Ann Am Thorac Soc. 2020. doi: 10.1513. Online ahead of print.*
12. *Kyle-Sidell C. COVID-19 Lung Injury and "Typical " ARDS: The danger of presumed Equivalency. Ann Am Thorac Soc. 2020;17: 1171-72.*
13. *Goebbels K, Gieseler U, Schöffl V, Küpper T. Cough and dyspnoea of an asthmatic patient at Mt. Kilimanjaro: a difficult differential diagnosis. Travel Med Infect Dis. 2010. ;8(1):22-8.*
14. *Ward MP, Milledge JS, West JB: High-altitude pulmonary edema. In: Ward et al.: High Altitude Medicine and Physiology, 5th edition; CRC Press, Taylor & Francis Group London 2013; 309-311.*
15. *Mounier R, Amonchot A, Caillot N, Gladine C, Citron B, Bedu M, Chirico E, Coudert J, Pialoux V. Pulmonary arterial systolic pressure and susceptibility to high altitude pulmonary edema. Respir Physiol Neurobiol 2011.15;179(2-3):294-9.*
16. *Lorenzo VF, Yang Y, Simonson TS, Nussenzveig R, Jorde LB, Prchal JT, Ge RL. Genetic adaptation to extreme hypoxia: study of high-altitude pulmonary edema in a three-generation Han Chinese family. Blood Cells Mol Dis. 2009;43(3):221-5.*
17. *Merz T, Maggiorini M: Mountaineering in extreme altitudes. In: A.G.Brunello/M. Walisser/U. Hefti (ed): Outdoor and Mountain Medicine.1st English edition, SAC Verlag, Bern, Switzerland 2014:206-25.*
18. *Mason RJ. Thoughts on the alveolar phase of COVID-19. Am J Physiol Lung Cell Mol Physiol 2020;319: 115-20.*
19. *Potus F, Mai V, Lebret M et al. Novel Insights on the Pulmonary Vascular Consequences of Covid-19. Am J Physiol Lung Cell Mol Physiol 2020;319:277-88.*
20. *Lax SF, Skok K, Zechner C, Kessler H et al. Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome: Results From a Prospective, Single-Center, Clinicopathologic Case Series. Ann Intern Med. 2020 14;M20-2566.*

21. *Bärtsch P, Haeberli A, Franciolli M et al. Coagulation and fibrinolysis in acute mountain sickness and beginning pulmonary edema. J App Phisiol. 1989;66:2136-44.*
22. *Kuebler WM, Jordt SE, Liedtke WB. Urgent reconsideration of lung edema as a preventable outcome in COVID-19: inhibition of TRPV4 represents a promising and feasible approach. Am J Physiol Lung Cell Mol Physiol. 2020 1;318(6):1239-43.*
23. *Swenson ER, Bärtsch P. High altitude pulmonary edema. Compr Physiol 2012;2:2753-73.*
24. *Swenson ER, Maggiorini M, Mongovin S et al. Pathogenesis of high-altitude pulmonary edema: inflammation is not an etiologic factor. JAMA 2002;287:2228-35.*
25. *Jensen JD, Vincent AL. High Altitude Pulmonary Edema. Treasure Island (FL): StatPearls Publishing; 2020 Jan.*
26. *Mahmudpour M, Roozbeh J, Keshavarz M et al. COVID-19 cytokine storm: The anger of inflammation. Cytokine 2020; 133:155151.*
27. *Quah P, Li A, Phua J. Mortality rates of patients with COVID-19 in the intensive care unit: a systematic review of the emerging literature. Crit Care 2020;24:285.*
28. *Chen Q, Xu L, Dai Y et al. Cardiovascular manifestations in severe and critical patients with COVID-19. Clin Cardiol 2020:1-7.*
29. *Thierry AR, Roch B. SARS-CoV2 may evade innate immune response, causing uncontrolled neutrophil extracellular traps formation and multi-organ failure. Clin Sci (Lond) 2020:134:1295-1300.*
30. *Berger MM, Schobersberger W, Rauch S. Von Äpfeln und Birnen: Covid-19-Pneumonie und Höhenlungenödem.Alpinmedizinischer Rundbrief. 63: Aug 2020: 12-3.*
31. *Bärtsch P, Maggiorini M, Ritter M et al. Prevention of high-altitude pulmonary edema by nifedipine. N Engl J Med 1991; 325:1284-89.*
32. *Gorjanc J, Morrison SA, McDonnell AC, Mekjavic IB. Koroška 8000 Himalayan expedition: digit responses to cold stress following ascent to Broadpeak (Pakistan, 8051 m). Eur J Appl Physiol. 2018. 118:1589-1597.*
33. *Gradišnik A. Sanje: Koroška 8000. Koroški alpinistični klub 2000, Črna na Koroškem. 2000. P 89.*
34. *Tan SC, Haines K, Zhang N. Beyond the ventilator: Rehabilitation for critically ill patients with coronavirus disease 2019. Aust Crit Care. 2020.33:485-87.*
35. *Lazzeri M, Lanza A, Bellini R, Bellofiore A, Cecchetto S, et al. Respiratory physiotherapy in patients with COVID-19 infection in acute setting: a Position Paper of the Italian Association of Respiratory Physiotherapists (ARIR). Arch Chest Dis. 2020. 26;90(1). doi: 10.4081.*
36. *Vitacca M, Carone M, Clini EM, Paneroni M et al. Joint Statement on the Role of Respiratory Rehabilitation in the COVID-19 Crisis: The Italian Position Paper. Respiration 2020.99:493-99.*
37. *Jiandani PM, Salagre BS, Kazi S et al. Preliminary Observations and Experiences of Physiotherapy Practice in Acute Care Setup of COVID 19: A Retrospective Observational Study. J Assoc Physicians India. 2020;68:18-24.*