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Review Article

Long COVID and its effects on the cardiovascular system: a literature review

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ABSTRACT

A significant cardiac burden exists post COVID-19. This is evident by persistent chest pain, palpitations, dyspnea, exertional fatigue, presence of new-onset heart failure or arrhythmia. Persistent COVID-19 symptoms in the cardiovascular system may be caused by a combination of processes that either increase inflammation or tamper with the autonomic nervous system. The inflammation can be caused by viral load persistence leading to tissue damage. The presence of cytokines and chemokines results in a state of hyper inflammation, immune exhaustion, organ damage during the infectious state and post-viral autoimmunity. The current review aims to discuss the risk factors, pathophysiology and treatment of the protracted form of COVID-19 in relation to the cardiovascular system.

Keywords: Long COVID, Long haulers syndrome, Chronic COVID-19, Post COVID-19 syndrome, Post-acute SARS-COV-2

INTRODUCTION

The COVID-19 pandemic has lasted for over a year and continuous effort to understand the disease process is still ongoing. The major variation is the intensity of symptoms experienced by different individuals irrespective of the onset of the disease. These symptoms are classified as mild, moderate, or severe. Initially, the disease course in patients with mild to moderate symptoms lasted for 2 weeks after which there was complete resolution of the disease.[1] Recently a group of patients has reported experiencing COVID-19 symptoms that persist for several weeks to months after the initial recovery of the illness.

This extensive form of COVID-19 is referred to by several names including long COVID, chronic COVID, long haulers, and post-acute COVID-19.[2] The national institute of health reached a consensus to name this entity the post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (PASC).[3] Most patients with the protracted form of COVID-19 are polymerase chain reaction (PCR) negative, therefore the disease state is a period between microbiological recovery and clinical recovery.[4]

The definition for post-acute COVID-19 is still evolving but universally it is defined as persistent symptoms or long-term complications beyond 4 weeks of acute onset of disease symptoms.[5]

The syndrome is further divided into two categories which include: sub-acute or ongoing symptomatic COVID-19 which involves symptoms present 4-12 weeks beyond acute COVID-19.[6] Chronic or post COVID-19 syndrome which includes symptoms persisting more than 12 weeks after the initial onset.[6]

The most common post-COVID-19 symptoms include fatigue, worsened quality of life, dyspnea, diarrhea, chest pain, cough, shortness of breath, and symptom of

increased anxiety.[4] The common cardiovascular symptoms may be due to vascular inflammation and autonomic dysfunction.[7,8]

METHODS OF LITERATURE SEARCH

An electronic search was made on Pubmed on the 07 of April 2022, using the search phrase COVID long haulers. The search yielded 78 results which were screened independently by both authors. For this review, articles were chosen based on their pertinence to the discussion. Key words during the screening process include long COVID, long haulers syndrome, chronic COVID-19, post COVID-19 syndrome, and post-acute SARS-COV-2.

EPIDEMIOLOGY

An observational cohort study from 38 hospitals in Michigan, United States, studied the outcomes of 1,250 patients two months following discharge. In this study, 6.7% of the patients died and 15.1% required re-admission. Out of the 488 patients who completed a telephone interview in this study, 32.6% reported persistent symptoms.[9]

Another study came from a post-acute outpatient service established in Italy, reporting persistence of symptoms in 87.4% of 143 patients discharged from the hospital after recovering from acute COVID-19. They had a mean follow-up of 60 days from the onset of the first day of symptoms. The main symptoms that were discovered were dyspnea, fatigue, joint pain, and chest pain.[10]

In France, a study focused on 150 survivors of non-critical COVID-19 and reported persistence of symptoms in two-thirds of individuals at 60 days of follow-up, with one-third reporting feeling worse than at the onset of acute COVID-19.[11]

A prospective cohort study from Wuhan, China, evaluating long-term consequences of acute COVID-19 was conducted by a comprehensive in-person evaluation of 1,733 patients at 6 months from symptom onset. The study utilized questionnaires, physical examination, 6-min walk tests, blood tests, pulmonary function tests, high-resolution computed tomography of the chest, and ultrasonography to evaluate post-acute COVID-19 end-organ injury. A majority of the patients (76%) reported at least one symptom. Patients reported having fatigue (63%), by sleep difficulties (26%) and anxiety/depression (23%).[12]

RISK FACTORS

Recent studies have shown an increased risk of the occurrence of post COVID-19 symptoms in the female sex. Suggested mechanisms for the rise in frequency include increased expression of angiotensin-converting enzyme-2 (ACE-2) and transmembrane protease serine 2 (TMPRSS-2) receptors in females compared to males, immunological differences (e.g., more expression of pro-inflammatory interleukin in females in comparison to males).[13]

Another risk factor reported by several studies is the correlation between initial acute COVID-19 severity and post-acute symptoms. These include intensive care unit (ICU) admissions, mechanical ventilation, or prolonged hospitalization.[14-16]

A four-month follow-up study of 434 COVID-19 survivors showed that patients presenting with at least 10 symptoms may have persistent manifestations in the post-acute phase.[17] Another study suggested that patients with five or more initial symptoms have an increased risk of developing long haulers symptoms.[18]

In summary, several studies have suggested that the main risk factors that may increase susceptibility to post-COVID symptoms are the female sex, increased severity of the initial infection, and the presence of more than five early symptoms.

PATHOPHYSIOLOGY

SARS-COV-2 has been known to affect multiple organ systems. This is due to the expression of the ACE-2 receptor in multiple organs.[19]

An autopsy study of 22 COVID-19 patients backs one of the most recent hypotheses explaining the persistence of viral particles in multiple organs (lungs, kidney, respiratory tract, and the heart) as a cause of long-term sequelae.[20] The presence of these viral particles could lead to a state of chronic inflammation in patients hence the manifestation of symptoms. This is a similar pattern that has been observed in the study of Chikungunya arthritis.[21]

Chronic viral infection is a phenomenon associated with immune exhaustion. Immune exhaustion is defined as the dysfunction of antigen-specific cells as a result of persistent stimulation.[22] In T-cell exhaustion, some common features include reduced production of cytokine, impaired clonal expansion, altered metabolism, upregulation of co-inhibitory receptors, impaired proliferation, and memory cell response.[23,24] Exhaustion of these T-cells is believed to lead to the persistence of viral particles in various cells. SARS-COV-2 viral particles may possess super antigens that bind to major histocompatibility complex-II (MHC-II) hence acting as potent T-cell mitogens.[25] In viral particle persistence, the T-cells are continually activated leading to a possible low-grade inflammatory state.

Viral-induced autoimmunity can also be a cause of post-acute manifestations of COVID. A study of 172 patients, noted that 52% of the participants with antiphospholipid antibodies of different isotypes.[26] The presence of antiphospholipid antibodies may lead to an increased frequency of thromboembolic events in COVID-19

patients. Another study showed 194 COVID-19 patients, with a high prevalence of autoantibodies against different proteins. Some of these proteins include cytokines, chemokines, complement proteins, immunomodulatory proteins, and metalloproteinases endothelial cell surface proteins. [27]

SARS-COV-2 infection has been associated with the reduction of ACE-2 receptors, leading to increased levels of angiotensin 2 in the bloodstream and an imbalance in the RAS pathway.[28]

In a study of a swine model, it was observed that RAS imbalance can cause diffused alveolar damage, increased coagulation, distorted lung perfusion, reduced blood oxygenation, increased pulmonary arterial pressure, and acute tubular necrosis; which are some shared similarities with the presentation of COVID.[29]

Tachycardia, palpitation, orthostatic intolerance, breathlessness, and chest pain are described as a consequence of autonomic dysfunction which can be attributed to the destruction of the nervous system by immune cells or by viral particles. These symptoms may also be caused by deconditioning, and hypovolemia.[30] A recent study measuring cardiac autonomic function and heart rate variability (HRV) found that increased HRV is associated with worse outcomes of long COVID.[31] The increased parasympathetic tone is associated with unresolved orthostatic symptoms including a recent diagnosis of postural orthostatic tachycardia (POTS).[31]

A cohort study found persistent myocardial inflammation which was evident by an increase in cardiac troponin as the cause of chest pain in long COVID patients.[32] Furthermore, a cross-sectional study involving 32 non hospitalized patients with post COVID symptoms described chronotropic incompetence as the cause of persistent fatigue and exercise intolerance.[33]

Chronotropic incompetence is defined as the limitation to increasing heart rate in response to metabolic demand which could be due to direct injury to the sinoatrial node or autonomic dysfunction.[33]

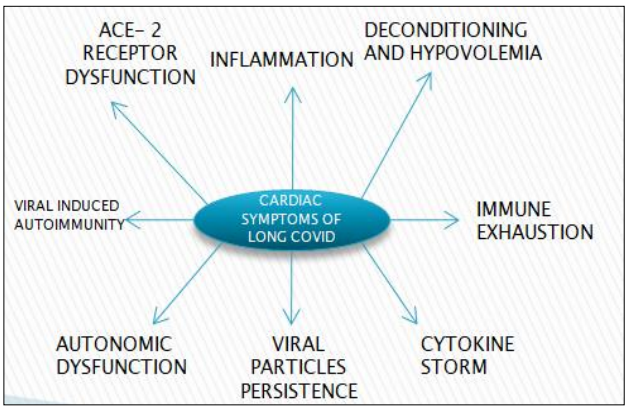

Figure 1: Pathophysiology of long COVID.

On a molecular level, maladaptation of the ACE-2 receptor pathway greatly expressed by cardiac tissues is responsible for the cardiac burden presented post-COVID.[1,33] Reentrant arrhythmia post-COVID may be due to myocardial fibrosis and an increase in cytokine expression of IL-1, IL-6, and TNFα.[6] These cytokines can prolong ventricular action potential and modulate cardiac myocyte expression.[6]

EVALUATION AND MANAGEMENT

The diagnosis of long COVID is a diagnosis of exclusion and physicians should approach each patient scenario with the intention of ruling out serious comorbidities or complications that might cause symptoms.[34] A multidisciplinary approach to management is advised and the evaluation starts with taking a detailed history, followed by a full physical examination. Blood tests and advanced imaging are ordered on a case-by-case basis.[1,4]

Chest pain post-COVID should be referred to cardiology when there is an unexplained cause or the patient is acutely unwell. Further investigation with electrocardiogram, computed tomography of the chest, and cardiac magnetic resonance imaging should be done when necessary.[35] The management of anticoagulation post-discharge varies but patients with a high risk of hypercoagulability are discharged with 10 days of extended thromboprophylaxis. If a new thrombotic event is diagnosed it should be treated following standard guidelines.[35] Finally, heart failure and left ventricular dysfunction post-COVID should be managed following standard guidelines.[35]

CONCLUSION

There is increased awareness that some COVID-19 symptoms may persist after microbiological resolution of the disease. Existing data has exhausted the pathophysiology and risk factors in relation to the cardiovascular system. Available treatment protocol advises a multidisciplinary approach while offering continuous care to the patient. The question yet to be answered is could these symptoms post COVID-19 be permanent or not. More research and data collection would be needed as the answer to this question would be relevant in counselling patients with these symptoms and in creating appropriate healthcare budget for this cause.

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REFERENCES

1. Vehar S, Boushra M, Ntiamoah P, Biehl M. Post-acute sequelae of SARS-CoV-2 infection: Caring for the 'long-haulers'. Cleve Clin J Med. 2021;88(5):267-72.
2. Ramakrishnan RK, Kashour T, Hamid Q, Halwani R, Tleyjeh IM. Unraveling the Mystery Surrounding

Post-Acute Sequelae of COVID-19. Front Immunol. 2021;12:686029.
3. Collins FS. NIH launches new initiative to study "Long COVID". National Institutes of Health. Available at: https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study-long-covid. Accessed on 23 February 2022.
4. Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: An overview. Diabetes Metab Syndr. 2021;15(3):869-75.
5. Kopanczyk R, Kumar N, Papadimos T. Post-Acute COVID-19 Syndrome for Anesthesiologists: A Narrative Review and a Pragmatic Approach to Clinical Care. J Cardiothorac Vasc Anesth. 2022;36(8):2727-37.
6. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601-15.
7. Christensen RH, Berg RMG. Vascular Inflammation as a Therapeutic Target in COVID-19 "Long Haulers": HIITing the Spot? Front Cardiovasc Med. 2021;8:643626.
8. Asarcikli LD, Hayiroglu Mİ, Osken A, Keskin K, Kolak Z, Aksu T. Heart rate variability and cardiac autonomic functions in post-COVID period. J Interv Card Electrophysiol. 2022;63(3):715-21.
9. Chopra V, Flanders SA, O'Malley M. Sixty-day outcomes among patients hospitalized with COVID-19. Ann Intern Med. 2021;174(4):576-8.
10. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324(6):603-5.
11. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect. 2020;81(6):4-6.
12. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397:220-32.
13. Bwire GM. Coronavirus: Why men are more vulnerable to COVID-19 than women? SN Compr Clin Med. 2020;2:874-6.
14. Taboada M, Cariñena A, Moreno E, Rodríguez N, Domínguez MJ, Casal A, et al. Post-COVID-19 functional status six-months after hospitalization. J Infect. 2021;82(4):31-3.
15. Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro F, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine. 2021;31:100683.
16. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol. 2021;93(2):1013-22.
17. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. Thorax. 2021;76(4):405-7.
18. Cirulli ET, Schiabor Barrett KM, Riffle S, Bolze A, Neveux I, Dabe S, et al. Long-term COVID-19 symptoms in a large unselected population. medRxiv. 2020.
19. The Lancet. Facing up to long COVID. Lancet. 2020;396(10266):1861.
20. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al. Multiorgan and Renal Tropism of SARS-Cov-2. New Engl J Med. 2020;383(6):590-2.
21. Zaid A, Gérardin P, Taylor A, Mostafavi H, Malvy D, Mahalingam S. Chikungunya Arthritis: Implications of Acute and Chronic Inflammation Mechanisms on Disease Management. Arthritis Rheumatol (Hoboken NJ). 2018;70(4):484-95.
22. Saeidi A, Zandi K, Cheok YY, Saeidi H, Wong WF, Lee CYQ, et al. T-Cell Exhaustion in Chronic Infections: Reversing the State of Exhaustion and Reinvigorating Optimal Protective Immune Responses. Front Immunol. 2018;9:2569.
23. Wherry EJ, Kurachi M. Molecular and Cellular Insights into T Cell Exhaustion. Nat Rev Immunol. 2015;15(8):486-99.
24. Schietinger A, Greenberg PD. Tolerance and Exhaustion: Defining Mechanisms of T Cell Dysfunction. Trends Immunol. 2014;35(2):51-60.
25. Scaglioni V, Soriano ER. Are Superantigens the Cause of Cytokine Storm and Viral Sepsis in Severe COVID-19? Observations and Hypothesis. Scandinavian J Immunol. 2020;92(6):e12944.
26. Zuo Y, Estes SK, Ali RA, Gandhi AA, Yalavarthi S, Shi H, et al. Prothrombotic Autoantibodies in Serum from Patients Hospitalized With COVID-19. Sci Trans Med. 2020;12(570):eabd3876.
27. Wang EY, Mao T, Klein J, Dai Y, Huck JD, Jaycox JR, et al. Diverse Functional Autoantibodies in Patients With COVID-19. Nature. 2021;595:283-8.
28. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A Crucial Role of Angiotensin Converting Enzyme 2 (ACE2) in SARS Coronavirus-Induced Lung Injury. Nat Med. 2005;11(8):875-9.
29. Rysz S, Al-Saadi J, Sjöström A, Farm M, CampocciaJalde F, Plattén M, et al. COVID-19 Pathophysiology May be Driven by an Imbalance in the Renin-Angiotensin-Aldosterone System. Nat Commun. 2021;12(1):2417.
30. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, Lim PB. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clin Med (Lond). 2021;21(1):63-7.
31. Asarcikli LD, Hayiroglu Mİ, Osken A, Keskin K, Kolak Z, Aksu T. Heart rate variability and cardiac

autonomic functions in post-COVID period. J Interv Card Electrophysiol. 2022;63(3):715-21.
32. Sanyaolu A, Marinkovic A, Prakash S, Zhao A, Balendra V, Haider N, Jain I, Simic T, Okorie C. Post-acute Sequelae in COVID-19 Survivors: an Overview. SN Compr Clin Med. 2022;4(1):91.
33. Jimeno-Almazán A, Pallarés JG, Buendía-Romero Á, Martínez-Cava A, Courel-Ibáñez J. Chronotropic Incompetence in Non-Hospitalized Patients with Post-COVID-19 Syndrome. J Clin Med. 2021;10(22):5434.
34. Leviner S. Recognizing the Clinical Sequelae of COVID-19 in Adults: COVID-19 Long-Haulers. J Nurse Pract. 2021;17(8):946-9.
35. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020;370:m3026.

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