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Mini Review

Cellular Pathology of COVID on the Heart: A Mini-Review

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Abstract

The course of COVID infections is mainly determined by cardiovascular functional impairment. Patients with preexisting cardiac disease have a significantly worse prognosis than patients with no known cardiac disease. The same applies to comorbidities such as diabetes mellitus and more advanced age. Cardiac involvement can be direct or indirect. Mild and fulminant myocarditis, myocardial scarring, post-infectious arrhythmias and stress cardiomyopathy, among others, can determine the prognosis of patients. ACE-II receptors play a major role in the initiation of endothelititis. Other receptors such as a disintegrin and metalloprotease-17 (ADAM-17), transmembrane protease serine type2 (TMPRSS2) and neuropilin 1 are also involved in this process. This review provides an overview of the cellular pathology of cardiac impairment in COVID infection.

Keywords: *COVID; Heart Failure*

Introduction

The high morbidity and mortality caused by coronavirus disease 2019 (COVID-19) includes cardiovascular functional impairment. Evidence suggests that COVID infection causes symptomatic cardiac insufficiency in patients with preexisting cardiac disease and troponin elevation in critically ill patients. The present work deals with the different cardiac manifestations of COVID infection and their pathophysiological basis.

Discussion

The reasons for a high morbidity and mortality caused by coronavirus disease 2019 (COVID-19) are multifactorial and include cardiovascular functional impairment. Evidence suggests that COVID infection causes symptomatic cardiac insufficiency in patients with preexisting cardiac disease, as well as a troponin elevation in critically ill patients [1,2]. Fulminant myocarditis, predicted to be responsible for 7% of the lethal outcome with cardiac involvement, has been demonstrated in autopsy studies and in 58% of patients after surviving a COVID infection with cardiac involvement by cardiovascular magnetic resonance imaging [3-5]. Other studies with cardiovascular mag-

netic resonance imaging have demonstrated persistent myocardial inflammation in up to 60% and irreversible myocardial injury such as scarring in 30.8% of cases [6,7].

Clinically, chest pain, persistent palpitations and an increased incidence of stress cardiomyopathy have been reported between 5%, 9% and 7.8%, respectively, by 60 days post a COVID infection [8-11].

In particular patients with cardiac involvement show increased cardiometabolic complications in the further course of the coronavirus disease. These are expressed in a reduced cardiac reserve and a dysregulation of the renin-angiotensin-aldosterone system (RAAS) [12].

The post-infectious arrhythmias frequently stem from a cardiomyopathy resulting from myocardial fibrosis [13].

The increased expression of cytokines such as IL-6, IL-1 and tumor necrosis factor-α, which persists even after a survived infection, leads to altered ventricular action potentials via modulation of cardiomyocyte ion channel expression. This in turn can lead to postural orthostatic tachycardia syndrome and sinus tachycardia due to the adrenergic modulation [14,15].

As a major receptor, SARS-CoV-2 interacts with ACE2, which occurs with a broad expression pattern in the heart, lung, gastrointestinal tract and kidney [16-19].

This binding alters the ACE2 signaling pathways to the extent that ACE2 is downregulated and angiotensin II levels increase. This pro-inflammatory mediator leads to direct endothelititis [20-22]. The process plays a critical role in the pathogenesis of multiorgan failure in COVID-19.

In this context, endothelial dysfunction results from discrepancies between reactive oxygen species production and nitric oxide reduction, remodeling of the left ventricle by differentiation of fibroblasts into myofibroblasts after secretion of transforming growth factor-beta (TGFβ) by monocytes and ultimately fibrosis [23-26].

In turn, endothelial dysfunction, in response to the infection, induces the coagulation system, leading to thrombotic complications [27,28]. In this regard, the increased incidence of thromboembolism during and post a COVID-19 infection emphasizes the role of endothelial dysfunction due to systemic vasculitis and endothelititis [28-32].

The thromboembolic complications that occur in rare cases post a COVID vaccination correspond in their pathophysiology to the autoimmune heparin-induced thrombocytopenia type-II termed mini-HIT, hence, they occur independently of vasculitis and endothelititis [23-35]. However, the tissue tropism of SARS-CoV-2 clearly diverges from the virus-host cell interaction via the ACE2 receptor, such that vasculitis from the heart occurs via the neuropilin-1 receptor, among others [36-38].

Neuropilin-1(NRP1) already plays a major role in cell survival, cell proliferation as well as angiogenesis in the context of malignancies [39,40].

A direct correlation with the NRP1 expression level [41,42] is furthermore suspected in the very high morbidity and mortality rate of COVID-19 in the elderly and in patients with comorbidities such as diabetes, cardiovascular disease and polycystic ovary syndrome (PCOS).

The binding and displacement of typical angiogenic ligands at the b1 domain of NRP1 by the S protein of SARS-CoV-2 may play a pathophysiological role in the severe vasculitis, which, in turn, may explain the severe course in patients with cardiovascular comorbidity [43,44].

A further receptor plays a crucial role in the COVID-19 virus, in particular in its extrapulmonary infestations, namely the transmembrane protease serine type2 (TMPRSS2). It cleaves the coronavirus spike (S) protein, which allows entry of the virus into the host cell by binding to the specific cellular receptor [45-47].

It is even suggested that the imbalance of the renin-angiotensin system (RAS) resulting from the interaction between angiotensin-converting enzyme 2 (ACE2), disintegrin and metalloproteinase domain 17 (ADAM17) and mainly with the expression of type II transmembrane serine protease (TMPRSS2) may explain the severe course [48,49].

One of the first signs of cardiac involvement is the elevation of cardiac troponin levels in 12-28% of cases, which has a high association with hypertension, coronary artery disease (CAD) and diabetes. This group of patients suffers from a severe course and has a higher mortality [50-52].

Patients with a pre-existing cardiovascular disease and elevated troponin T have the highest mortality [53-56] whilst patients without cardiovascular disease and without troponin T elevation have the best prognosis for cardiac involvement after COVID infection [53].

A similar prognostic factor is serial N-terminal B-type natriuretic peptide (NT-proBNP), the elevation of which is associated with unequivocally poor survival [54].

Additionally, several studies have shown a clear correlation between troponin T level and NT-proBNP, C-reactive protein (CRP), creatine kinase and myoglobin, the elevation of which is associated with significantly higher mortality as a sign of a more severe systemic inflammation [56-58].

SARS-CoV-2 infection induces the expression of a number of proinflammatory cytokines such as tumor necrosis factor superfamily TNF superfamily member 10 (TNFSF), CC chemokine ligand (CCL)2, CXC chemokine CXCL2, CXCL1, IL33, CCL3L1 in BALF, neuregulin1, amphiregulin among others, which trigger a so-called cytokine storm [59-63].

This leads to a myocardial ischemia, both, directly mainly through ACE2 and indirectly through hypoxia induced via severe pulmonary inflammation [64-67].

The higher susceptibility to COVID infection in men may be explained, at least in part, by a higher plasma level of ACE2 than in women, which results from activation of a disintegrin and metalloprotease-17 (ADAM-17). The resulting renin-angiotensin overactivity has cardiotoxic effects [68,69].

A similar mechanism with the excessive ACE2 expression is hypothesized for the severe course in the elderly. The comorbidity often presents in vascular disease, such as diabetes, hyperlipidemia and arterial hypertension and it may also indirectly influence infection-related mortality by altering the immune response [70,71].

In summary, cardiac involvement secondary to COVID infection may manifest as acute coronary syndrome, myocardial infarction, heart failure, cytokine storm, myocardial dysfunction, myocarditis and stress cardiomyopathy [72].

Diagnostic measures include determination by state trajectory of TnT concentration and ECG changes (defined as ST-segment elevation/ST-T0); coronary angiography; hemodynamic stress quantified by BNP and NT-proBNP concentrations; serum CK-MB; elevated plasma d-dimer, TnT, LDH and IL levels; endomyocardial biopsy in selected cases; and cardiac imaging patterns [73-76].

The drugs initially used for prophylaxis of COVID-19 infection, such as hydroxychloroquine and azithromycin, resulted in QT prolongation, severe arrhythmias and rarely sudden death as rare side effects, especially in female and elderly patients [77,78].

Thus, utmost caution is advised in the use of hydroxychloroquine and azithromycin due to the serious adverse side effects [79,80].

Conclusion

The multiple cardiovascular manifestations in COVID-19 infection significantly influence the high morbidity and mortality. Therefore, cardiologists must be involved at a very early stage in the management and treatment of patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

Bibliography

1. Shi S., *et al*. "Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China". *JAMA Cardiology* 5.7 (2020): 802-810.
2. Guo T., *et al*. "Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19)". *JAMA Cardiology* 5.7 (20207): 811-818.
3. Chen, L., *et al*. "The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2". *Cardiovasc Research* 116.6 (2020): 1097-1100.
4. Shi S., *et al*. "Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China". *JAMA Cardiology* b5.7 (2020): 802-810.
5. Xu Z., *et al*. "Pathological findings of COVID-19 associated with acute respiratory distress syndrome". *The Lancet Respiratory Medicine* 8.4 (2020): 420-422.
6. Carvalho-Schneider C Laurent, E., *et al*. "Follow-up of adults with noncritical COVID-19 two months after symptom onset". *Clinical Microbiology and Infection* 27.2 (2021): 258-263.
7. Huang C., *et al*. "6-month consequences of COVID-19 in patients discharged from hospital: a cohort study". *Lancet* 397.10270 (2021): 220-232.
8. Jabri A., *et al*. "Incidence of stress cardiomyopathy during the coronavirus disease 2019 pandemic". *JAMA Network Open* 3.7 (2020): e2014780.
9. Wu Q., *et al*. "Altered lipid metabolism in recovered SARS patients twelve years after infection". *Scientific Reports* 7.1 (2017): 9110.
10. Liu PP., *et al*. "The science underlying COVID-19: implications for the cardiovascular system". *Circulation* 142 (2020): 68-78.
11. Lazzerini PE., *et al*. "Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies". *Nature Reviews Immunology* 19.1 (2019): 63-64.
12. Agarwal AK., *et al*. "Postural orthostatic tachycardia syndrome". *Postgraduate Medical Journal* 83.981 (2007): 478-480.
13. Bogoch II., *et al*. "Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel". *Journal of Travel Medicine* 27 (2020): taaa008.
14. Lu H., *et al*. "Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle". *Journal of Medical Virology* 92.4 (2020): 401-402.

15. Guo YR., *et al*. "The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak—an update on the status". *Military Medical Research* 7.1 (2020): 11.

16. Desai AD., *et al*. "Management of arrhythmias associated with COVID-19". *Current Cardiology Reports* 23.2 (2021).

17. Cascella M., *et al*. "Features, evaluation, and treatment coronavirus (COVID-19), in StatPearls [internet]. Treasure Island: StatPearls (2021).

18. Li W., *et al*. "Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus". *Nature* 426 (2003): 450-454.

19. Groß S., *et al*. "SARS-CoV-2 receptor ACE2-dependent implications on the cardiovascular system: from basic science to clinical implications". *Journal of Molecular and Cellular Cardiolog* 144 (2020): 47-53.

20. Cooke JP. "The endothelium: a new target for therapy". *Vascular Medicine* 5.1 (2000): 49-53.

21. Pons S., *et al*. "The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection". *Crit Care* 24.1 (2020): 353.

22. Schiffrin EL., *et al*. "Hypertension and COVID-19". *American Journal of Hypertension* 33.5 (2020): 33-373.

23. Richardson S., *et al*. "Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area". *The Journal of the American Medical Association* 323.20 (2020): 2052-2059.

24. Dutka M., *et al*. "Various aspects of inflammation in heart failure". *Heart Failure Reviews* 25 (2020): 537-548.

25. Becker RC. "COVID-19 update: Covid-19-associated coagulopathy". *The Journal of Thrombosis and Thrombolysis* 50.1 (2020): 54-67.

26. Dolhnikoff M., *et al*. "Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19". *Journal of Thrombosis and Haemostasis* 18.6 (2020): 1517-1519.

27. Danzi GB., *et al*. "Acute pulmonary embolism and COVID-19 pneumonia: a random association?" *European Heart Journal* 41.19 (2020): 1858.

28. Poissy J., *et al*. "Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence". *Circulation* 142.2 (2020): 184-186.

29. Ullah W., *et al*. "COVID-19 complicated by acute pulmonary embolism and right-sided heart failure". *JACC: Case Reports* 2.9 (2020): 1379-1382.

30. Schultz NH., *et al*. "Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination". *The New England Journal of Medicine* (2021): NEJMoa2104840.

31. Greinacher A., *et al*. "Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination". *The New England Journal of Medicine* (2021): NEJMoa2104840.

32. Cantuti-Castelvetri, L., *et al*. "Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity". *Science* 370.6518 (2020): 856-860.

33. Daly JL., *et al*. "Neuropilin-1 is a host factor for SARS-CoV-2 infection". *Science* 370.6518 (2020): 861-865.

34. Li Z and Buck M. "Neuropilin-1 assists SARS-CoV-2 infection by stimulating the separation of spike protein domains S1 and S2". *Bio Rxiv* (2021).

35. Elpek GÖ. "Neuropilins and liver". *World Journal of Gastroenterology* 21.23 (2015): 7065-7073.

36. Roy S., *et al*. "Multifaceted role of neuropilins in the immune system: potential targets for immunotherapy". *Frontiers in Immunology* 8 (2017): 1228.

37. Nasarre C., *et al*. "Peptide-based interference of the transmembrane domain of neuropilin-1 inhibits glioma growth in vivo". *Oncogene* 29.16 (2010): 2381-2392.

38. Moin ASM., *et al*. "The relationship of soluble neuropilin-1 to severe COVID-19 risk factors in polycystic ovary syndrome". *Metabolism Open* 9 (2021): 100079.

39. Mayi BS., *et al*. "The role of Neuropilin-1 in COVID-19". *PLoS Pathology* 17.1 (2021): e1009153.

40. Machhi J., *et al*. "The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections". *Journal of Neuroimmune Pharmacology* 15.3 (2020): 359-386.

41. Li W., *et al*. "Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus". *Nature* 426 (2003): 450-454.

42. Lan J., *et al*. "Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor". *Nature* 581.7807 (2020): 215-220.

43. Iwata-Yoshikawa N., *et al*. "TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection". *Journal of Virology* 93.6 (2019): e01815-01818.

44. Li F., *et al*. "Structure of SARS coronavirus spike receptor-binding domain complexed with receptor". *Science* 309 (2005): 1864-1868.

45. Kuba K., *et al*. "Trilogy of ACE2: A peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters". *Pharmacology and Therapeutics* 128.1 (2010): 119-128.

46. Crackower MA., *et al*. "Angiotensin-converting enzyme 2 is an essential regulator of heart function". *Nature* 417 (2002): 822-828.

47. Lambert DW., *et al*. "Tumor Necrosis Factor-α Convertase (ADAM17) Mediates Regulated Ectodomain Shedding of the Severe-acute Respiratory Syndrome-Coronavirus (SARS-CoV) Receptor, Angiotensin-converting Enzyme-2 (ACE2)". *Journal of Biological Chemistry* 280 (2005): 30113-30119.

48. Epelman S., *et al*. "Detection of Soluble Angiotensin-Converting Enzyme 2 in Heart Failure". *Journal of the American College of Cardiology* 52 (2008): 750-754.

49. Sama IE., *et al*. "Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors". *European Heart Journal* 41 (2020): 1810-1817.

50. Oudit GY and Pfeffer MA. "Plasma angiotensin-converting enzyme 2: novel biomarker in heart failure with implications for COVID-19". *European Heart Journal* 41 (2020): 1818-1820.

51. Satoh M., *et al*. "Expression of tumor necrosis factor-alpha-converting enzyme and tumor necrosis factor-alpha in human myocarditis". *Journal of the American College of Cardiology* 36 (2000): 1288-1294.

52. Satoh M., *et al*. "Increased expression of tumor necrosis factor-α converting enzyme and tumor necrosis factor-α in peripheral blood mononuclear cells in patients with advanced congestive heart failure". *European Journal of Heart Failure* 6 (2004): 869-875.

53. Chen C., *et al*. "Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19". *Zhonghua Xin Xue Guan Bing Za Zhi* 48.7 (2020): 567-571.

54. Bonow RO., *et al*. "Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality". *JAMA Cardiology* 5.7 (2020): 751-753.

55. Xiong TY., *et al*. "Coronaviruses and the cardiovascular system: acute and long-term implications". *European Heart Journal* 41.19 (2020): 1798-1800.

56. Colafrancesco S., *et al*. "COVID-19 gone bad: a new character in the spectrum of the hyperferritinemic syndrome?" *Autoimmunity Reviews* 19.7 (2020): 102573.

57. Ruan Q., *et al*. "Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China". *Intensive Care Medicine* 46 (2020): 846-848.

58. Wu C., *et al*. "Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China". *JAMA Internal Medicine* 180.7 (2020): 934-943.

59. Behrens EM and Koretzky GA. "Review: cytokine storm syndrome: looking toward the precision medicine era". *Arthritis and Rheumatology* 69.6 (2017): 1135-1143.

60. Azkur AK., *et al*. "Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19". *Allergy* 75.7 (2020): 1564-1581.

61. Zheng YY., *et al*. "COVID-19 and the cardiovascular system". *Nature Reviews Cardiology* 17.5 (2020): 259-260.

62. Alexander LK., *et al*. "An experimental model for dilated cardiomyopathy after rabbit coronavirus infection". *The Journal of Infectious Diseases* 166.5 (1992): 978-985.

63. Small JD., *et al*. "Rabbit cardiomyopathy associated with a virus antigenically related to human coronavirus strain 229E". *The American Journal of Pathology* 95 (1979): 709-729.

64. Sama IE., *et al*. "Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors". *European Heart Journal* 41.19 (2020): 1810-1817.

65. Ingraham NE., *et al*. "Understanding the renin-angiotensin-aldosterone-SARS-CoV-Axis: a comprehensive review". *European Heart Journal* 56.1 (2020): 2000912.

66. Palau V., *et al*. "ADAM17 inhibition may exert a protective effect on COVID-19". *Nephrology Dialysis Transplantation* 35.6 (2020): 1071-1072.

67. Ren J., *et al*. "Estrogen upregulates MICA/B expression in human nonsmall cell lung cancer through the regulation of ADAM17". *Cellular and Molecular Immunology* 12.6 (2015): 768-776.

68. Rizzo P., *et al*. "COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm?" *Basic Research in Cardiology* 115.3 (2020): 31.

69. Zidar DA., *et al*. "Association of lymphopenia with risk of mortality among adults in the US general population". *JAMA Network Open* 2.12 (2019): e1916526.

70. Saltiel AR and Olefsky JM. "Inflammatory mechanisms linking obesity and metabolic disease". *Journal of Clinical Investigation* 127.1 (2017): 1-4.

71. Driggin E., *et al*. "Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic". *Journal of the American College of Cardiology* 75.18 (2020): 2352-2371.

72. Zhang L., *et al*. "Bedside Focused Cardiac Ultrasound in COVID-19 from the Wuhan Epicenter: The Role of Cardiac Point-of-Care Ultrasound, Limited Transthoracic Echocardiography, and Critical Care Echocardiography". *Journal Info. American Society of Echocardiography* 33.6 (2020): 676-682.

73. Choi Y., *et al*. "Risk evaluation of azithromycin-induced QT prolongation in real-world practice". *BioMed Research International* (2018): 1574806.

74. Sears SP., *et al*. "Incidence of sustained ventricular tachycardia in patients with prolonged QTc after the administration of azithromycin: a retrospective study". *Drugs Real World Outcome* 3.1 (2016): 99-105.

75. Huang BH., *et al*. "Azithromycin-induced torsade de pointes". *Pacing and Clinical Electrophysiology* 30.12 (2007): 1579-1582.

76. Kezerashvili A., *et al*. "Azithromycin as a cause of QT-interval prolongation and torsade de pointes in the absence of other known precipitating factors". *The Journal of Interventional Cardiac Electrophysiology* 18.3 (2007): 243-246.

77. Ray WA., *et al*. "Azithromycin and the risk of cardiovascular death". *The New England Journal of Medicine* 366.20 (2012): 1881-1890.

78. Zhang M., *et al*. "Electrophysiologic studies on the risks and potential mechanism underlying the proarrhythmic nature of azithromycin". *Cardiovascular Toxicology* 17.4 (2017): 434-440.

79. Capel RA., *et al*. "Hydroxychloroquine reduces heart rate by modulating the hyperpolarization-activated current If: novel electrophysiological insights and therapeutic potential". *Heart Rhythm* 12.10 (2015): 2186-2194.

80. Malviya A. "Ventricular arrhythmia risk due to chloroquine/hydroxychloroquine treatment for COVID-19: Should it be given". *Indian Heart Journal* 72.2 (2020): 131-132.

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