Review Article

Aastha Pal, Ashok Kumar Ahirwar*, Apurva Sakarde, Priyanka Asia, Niranjana Gopal, Sana Alam, Kirti Kaim, Pradeep Ahirwar and Smita R. Sorte

COVID-19 and cardiovascular disease: a review of current knowledge

<https://doi.org/10.1515/hmbci-2020-0052>

Received July 27, 2020; accepted January 14, 2021;
published online February 4, 2021

Abstract: The uncontrolled spread of the COVID-19 pandemic which originated in China created a global turmoil. While the world is still busy figuring out a cure for the deadly disease, scientists worked out on many theories and conducted several studies to establish a relationship between the infection and other known diseases. Cardiovascular diseases (CVD) are one of the major complications of this infection after the respiratory manifestations. Individuals with cardiovascular complication are said to be more susceptible to acquiring the infection because the novel coronavirus uses the ACE2 receptor for its entry inside the cell and there is a high level of ACE2 expression in individuals with cardiovascular complications because of the enzyme's anti-hypertrophic, anti-fibrotic and anti-hypertensive effects on the heart. Individuals who belong to the older age group are also more susceptible. Knowing the above information, it might seem that using ACE2 inhibitors would help to slow or

prevent the entry of the novel coronavirus but it would also at the same time prove to have deleterious effects on the cardiovascular system as the protective functions of ACE2 would be lost. While the search for a cure still continues it has been stated many a times that the conditions might worsen with time and the only way to keep ourselves and our family safe would be to follow the appropriate social distancing methods and get a COVID test if we experience any of the major symptoms.

Keywords: cardiovascular disease; COVID-19; SARS-CoV-2.

Introduction

The outbreak of the deadly coronavirus disease COVID-19 has created a global health crisis and has made a huge impact on the quality of life all around the world. According to the World Health Organization WHO, there are 15,257,287 confirmed cases of the infection globally with 628,240 deaths as of 24 July 2020 [1]. The time line of evolution of COVID-19 pandemic is shown in Figure 1.

General introduction to the coronavirus

Coronaviruses are classified under the subfamily *Orthocoronavirinae* in the family *Coronaviridae*, order *Nidovirales* and realm *Riboviria* [2]. According to the cryo-EM images of coronavirus particles they are enveloped, spherical and ellipsoidal virions. Cone-shaped spikes emerge in a fringe like pattern from the viral membrane [3]. They are classified with toroviruses, arteriviruses, and roniviruses in the order *Nidovirales*. Coronaviruses derive their name from the protruding oligomers of spike glycoprotein (S) which form a coronal fringe around the virus.

The genome of the coronavirus is nonsegmented, single stranded, and positive sense RNA. Its size is in the range of 27–32 kb and is comparatively larger than other RNA viruses.

***Corresponding author: Dr. Ashok Kumar Ahirwar**, MD, Assistant Professor, Department of Biochemistry, All India Institute of Medical Sciences, Nagpur, Maharashtra, 441108, India,

Mobile: +91 9654210832, E-mail: drashoklhmc@gmail.com

Aastha Pal, All India Institute of Medical Sciences, Nagpur, Maharashtra, India, E-mail: aastha2pal@gmail.com

Apurva Sakarde, Priyanka Asia and Niranjana Gopal, Department of Biochemistry, All India Institute of Medical Sciences, Nagpur, Maharashtra, India, E-mail: aforapurva@gmail.com (A. Sakarde), priyanka1asia@gmail.com (P. Asia), gopal.niranjana@gmail.com (N. Gopal)

Sana Alam, Department of Biochemistry, Hamdard Institute of Medical Sciences and Research, New Delhi, India, E-mail: sana2k2@gmail.com

Kirti Kaim, Department of Ophthalmology, Indira Gandhi ESI Hospital, New Delhi, India, E-mail: kirti.kaim@gmail.com

Pradeep Ahirwar, Indira Gandhi Hospital, Bhopal, Madhya Pradesh, India, E-mail: pradeepahirwar21@gmail.com

Smita R. Sorte, Department of Physiology, All India Institute of Medical Sciences, Nagpur, Maharashtra, India, E-mail: drsmyta@gmail.com

Figure 1: Timeline of COVID-19 pandemic.

The genome also contains a 5' cap along with a 3' poly(A) tail enabling it to act as a mRNA for translation of the replicase polyproteins. The ribonucleoprotein (RNP) core consists of nucleoprotein particles and positive stranded genome. The virus' membrane has a triple pass transmembrane glycoprotein (M) necessary for virus assembly [4].

General symptoms of coronavirus infection

From the various ongoing studies, it has been found that it takes a period of about 5–6 days from exposure to the onset of symptoms. However, this is not a generalized rule as the symptoms may appear as early as three days from exposure to as long as 13 days. Hence incubation period of COVID-19 is highly variable. According to a study conducted by Nanshan Chen et al. the various symptoms of coronavirus infection are fever, cough, myalgia or fatigue, shortness of breath, muscle ache, headache, sore throat, rhinorrhea, hemoptysis, chest pain, nausea, and vomiting as shown in Figure 2 [5].

The severity of the coronavirus infection ranges from mild to severe. Some individuals might show a combination of the previous mentioned symptoms while some might be asymptomatic. For several weeks from January to February, an early release study from China found that approximately 13% of transmissions are from asymptomatic persons. Based on the currently available data and the clinical knowledge a certain fraction of individuals are believed to be more susceptible and are at a higher risk for severe illness from COVID-19. This includes individuals of any age with asthma (moderate to severe), chronic lung disease, diabetes, serious heart conditions, chronic kidney disease being treated with dialysis, severe obesity, liver disease, an immunocompromised person, and individuals aged 65 years and older.

Figure 2: Symptoms of COVID-19.

Complications of COVID-19 infections

As shown in Figure 3, COVID-19 is associated with many complications which may lead to adverse outcome.

Acute respiratory distress syndrome (ARDS): according to a study conducted on 201 COVID-19 patients with confirmed pneumonia it was found out that major risk factors for ARDS development are old age, neutrophilia, organ and coagulation dysfunction (higher lactate dehydrogenase) and higher D-dimer. High fever may also be another factor [6].

Acute liver damage: various research and data obtained by the studies carried out in China shows that the critically ill patients have a high risk for liver damage. The injury can be because of direct viral infection of hepatocytes, immune related injury, or drug hepatotoxicity.

Acute kidney injury: though not a very common complication it might become a problem in the later stages. Chances of developing acute kidney injury might be old age or previous history of the same, heart failure, hepatic disease, and diabetes [7].

Neurological complications: in a study conducted on 214 COVID-19 patients of Wuhan it was found that 36.4% of the patients had some or the other neurological complications. These were more common in individuals of older age with underlying disorders. Acute cerebrovascular

Figure 3: Various complications in COVID-19.

changes, impaired consciousness, ataxia, seizures, and skeletal muscle injury were the main manifestations [8].

Pregnancy related complications: in a study conducted on pregnant women it was found that some of them developed symptoms such as fever and cough before delivery while some after. Some of them also presented with myalgia, sore throat, and malaise. First symptoms in the newborn were shortness of breath along with that liver, fetal distress, rapid heart rate, vomiting, fever thrombocytopenia, and deaths was also reported in some cases [9, 10].

Toxic shock syndrome and Kawasaki disease: these have been found to be the recent and rare complications of the infection particularly in children. New reports from USA and Europe have shown that there might be a collection of symptoms like lengthy fevers, low blood pressure, rashes, GI disturbance, and inflammation of heart and arteries. Deaths have also been reported due to these complications [11].

General lab findings of corona virus infection

The data for the clinical lab findings mentioned here are taken from a retrospective study conducted by G. Zhang, J. Zhang et al. on 95 patients with laboratory confirmed 2019 novel coronavirus pneumonia in Wuhan. Higher temperature, blood leukocyte count, alanine aminotransferase activity, aspartate aminotransferase activity, hydroxybutyrate dehydrogenase activity, lactate dehydrogenase activity, and creatine kinase activity were related to severe 2019 novel coronavirus pneumonia and composite endpoint, and so were lower lymphocyte count, lymphocyte percentage and total protein level. Age below 40 or above 60 years old, male, higher creatinine level, and lower platelet count also seemed related to severe 2019 novel coronavirus pneumonia [12].

COVID-19 and cardiovascular diseases

Cardiovascular diseases (CVDs) related to COVID-19 infections as shown in Figure 4 are due to:

Direct myocardial injury: virus entry might lead to disturbance in the ACE2 signaling pathways which might be a reason for acute myocardial injury.

Systemic inflammation: acute systemic inflammatory response and cytokine storm are some of the most severe effects of the viral infection. These changes might lead to multi-organ failure. Clinical lab findings of severely ill patients show high level of circulatory cytokines.

Altered myocardial demand-supply ratio: increased cardiometabolic demand associated with the systemic infection coupled with hypoxia caused by acute respiratory illness can impair myocardial oxygen demand-supply relationship and lead to acute myocardial injury [13].

Arrhythmias: both tachy and bradycardia are seen in COVID-19 infection.

Role of ACE2 in cardiovascular system

ACE2 was discovered as a homolog of ACE1 in 2000. It is a monocarboxypeptidase that converts Ang I to a non-peptide Ang 1–9, and Ang II to a heptapeptide Ang 1–7. ACE2 is a type I transmembrane protein with an extracellular

N-terminal domain containing the catalytic site and an intracellular C-terminal tail. Similar to ACE1, it is an ectoenzyme with its catalytic site facing towards the circulating vasoactive peptides. In the heart ACE2 is found abundantly in cardiomyocytes, cardiac fibroblasts and cardiac endothelial cells [14]. The action of a disintegrin and metalloproteinase ADAM-17 also known as Tumor necrosis factor- α Converting Enzyme (TACE) causes the shedding of many substances from its surface. ADAM-17 mediated proteolysis leads to the release of an enzymatically active and soluble domain of the enzyme. The RAS is an important family for maintenance of renal and cardiovascular functions. Renin, a protease, cleaves off a decapeptide from the amino terminal of a plasma protein of liver angiotensinogen. This decapeptide angiotensin I is inactive and is converted to active angiotensin II by the enzyme ACE1. The primary function of ACE2 is to convert this Ang II to Ang 1–7. In 2003, an endogenous orphan receptor, Mas (MasR), was identified as the Ang 1–7 receptor [15]. ACE2/angiotensin1-7/MasR is another limb of the RAS whose main function is to act as the antagonists of the activated RAS system. While angiotensin II is known to have mainly vasoconstrictive, proinflammatory and pro-fibrotic effects, Ang 1–7 are known to exhibit vasodilating functions along with anti-hypertrophic, anti-fibrotic, anti-hypertensive effects. ACE2 is also responsible for reducing cardiac fibrosis and managing MI induced cardiac dysfunction.

ACE2 and COVID-19

ACE2 receptors are responsible for the entry of three strains of coronaviruses into the cell: SARS-CoV, NL-63, and SARS-CoV2 [16]. ACE2 receptors are found in heart, lungs, vessels, gut, kidney, testis, and brain. The enormous surface area of the alveolar endothelial cells might be one of the reasons for the high expression of ACE2 in lungs, and pulmonary dysfunctions being the major effect of SARS-CoV2 on the human body.

Binding of the novel coronaviruses onto the receptors of ACE2 are facilitated by the viral spike protein which is processed by the protease TMPRSS2. The spike protein is a 1,273 amino acid long protein and belongs to the virus envelope. It protrudes outwards with a 'corona' like appearance to the ACE2 receptors [16]. The N-terminal portion of the spike protein S1 interacts with the extracellular domain of ACE2 receptors. Cleavage takes place between the S1 and S2 units which occurs with the help of TMPRSS2. After the cleavage S1 portion is detached and the remaining viral S2 subunit undergoes clathrin dependent endocytosis. Once the virus has taken entry in the host's cell, the viral RNA is released and it

Figure 4: The pathophysiology of cardiovascular involvement in COVID-19.

uses the host's cellular machinery for the synthesis of more infectious progeny.

ACEIs and ARBs: their dual role in COVID-19

ACE inhibitors and angiotensin receptor blockers (ARBs) are a group of medicines which are by and large used for the treatment of high blood pressure and heart failure. ACEIs reduce the activity of renin angiotensin-aldosterone system (RAAS) and inhibit the conversion of angiotensin I (ATI) to angiotensin II (ATII). In vitro studies demonstrate that ACEIs and ARBs can significantly increase or upregulate the expression and activity of ACE2 enzyme which is highly expressed in the heart. While the role of ACE2 in converting ATII to AT 1–7 and preventing ATII induced myocardial hypertrophy, diastolic dysfunction and myocardial fibrosis is one side of the coin, its detrimental role of latching the spike protein of SARS-CoV2 onto its receptor cannot be ignored. Enalapril can restore left ventricular ACE2 expression levels in rats with heart failure. Losartan and olmesartan can increase the expression of ACE2 mRNA in the heart of rats after myocardial infarction. It was found that lisinopril can increase the level of ACE2 mRNA but not the activity of ACE2 in the heart of normal Lewis rats, whereas losartan can simultaneously increase the mRNA expression as well as the protein activity of ACE2 in the heart of normal Lewis rats. A debatable question which arises here is that whether these medications make individuals more susceptible to COVID-19 infection. The medicines are acting as a double edged sword by ameliorating the heart and lung damage caused by the virus and increasing the ACE2 receptors hand in hand. Studies suggest that discontinuing their use would not be the best option as their beneficial effects outweigh the theoretical risks [17].

Possible treatment methods

The number of confirmed coronavirus cases has crossed 4 million and is continuing to increase. With this the healthcare system around the globe is overwhelmed and we are in a more frenzied need than ever before for a safe and effective treatment for COVID-19.

Though there is no specific drug which has yet been proven to be 100% effective in the treatment process, doctors all around the world are trying different therapies and are also recommending drugs which may not be a cure but help ameliorate the effects of the infection.

Dexamethasone: it is the most recent drug which claims to reduce the mortality rate by one third in critically ill patients after a study group conducted its clinical trials in UK under RECOVERY (Randomized Evaluation of COVID-19 Therapy). It is a potent synthetic steroid and has been in use since a long time for cancer, some specific forms of tuberculosis, mountain sickness, arthritis, and severe asthma. It is a powerful anti-inflammatory agent. Drugs like remdesvir try to inhibit the virus from replicating within the host cell whereas dexamethasone counteracts the aggravated inflammatory response. A heightened inflammatory response is seen during the last stages of the infection which can be one of the reasons why the drug is used in critically ill patients. However along with the good there is also bad. Dexamethasone is also an immunosuppressive drug and it further reduces the already low T-lymphocytes in blood. Other side effects include dizziness, irregular heartbeat, brittle bones, fractures, increased blood sugar levels etc. [18, 19].

Vaccine development

With a huge fraction of individuals around the world locked inside their houses, scientists and researchers are working tirelessly and running a race against time to find a cure for the deadly coronavirus. The World Health Organization has already said that it might take a time period of about 12–18 months to develop a vaccine and with the number of deaths across the world reaching a monstrous figure of over 309,001 many fears that individuals must learn to live with the virus.

Now a remarkable point to be discussed here is that the Chinese researchers were able to decode the genetic code of the virus as early as in January within weeks of its emergence but then what's the hold up? "Essentially, you can speed up the vaccine development process to respond to a pandemic, but you don't want to speed it up so much that you allow a bad vaccine to enter the market", explained Dr. Greg Poland, director of the Mayo Clinic's Vaccine Research Group.

It requires a whole lot of resources and effort to develop a vaccine which is fit for human use and there are a number of candidates around the world in the race to develop this vaccine.

- a. Moderna vaccine: In the US, the Massachusetts based biotech company Moderna is developing an RNA based vaccine in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID). The vaccine has already conducted phase 1 trials and also received permissions for the phase 2 trials.

- b. The Oxford University: The University of Oxford has developed a vaccine candidate 'ChAdOx1CoV-19'. It uses a weakened strain of common cold virus (adenovirus) and is combined with the genetic material of SARS-CoV-2. This will enable the body to identify the spike protein of the coronavirus. It is currently in the clinical trial phase 2/3.
- c. Beijing based Sinovac Biotech: Chinese scientists claim to have successfully tested a potential vaccine for the coronavirus in monkeys. The researchers injected the monkeys with the potential vaccine 'PiCoVacc' and these monkeys were then later exposed to the novel coronavirus and it was found that those injected with a dose of the potential vaccine were largely protected from the virus [20].
- d. Pfizer and BioNtech: US-based Pfizer pharmaceutical company and its German partner are working together on four RNA vaccine candidates. They have also begun clinical trials of their vaccine candidate BNT162 based on specially designed messenger RNA.

Apart from the aforementioned vaccine candidates, Johnson and Johnson vaccine, Ad5-nCoV by Chinese vaccine maker CanSino Biologics Inc, Sanofi a French pharmaceutical company are the other big players in the development of potential vaccines.

Acknowledgments: We are thankful to Dr. Satyendra Chandra Tripathi, Assistant Professor, Department of Biochemistry, All India Institute of Medical Sciences, Nagpur, Maharashtra, 441108, India.

Research funding: None.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: None to declare.

Informed consent: Not applicable.

Ethical approval: Not applicable.

References

1. WHO Coronavirus Disease (COVID-19) dashboard. Available from: https://covid19.who.int/?gclid=Cj0KCQjwirz3BRD_ARIsAlmf7LN3MIMU4Q89WeSruACALVI2WwAuuT5YqzUy-43GaqLBpjkfssOG7V4aArXyEA [Accessed 24 Jul 2020].
2. de Groot RJ, Baker SC, Baric R, Enjuanes L, Gorbalenya AE, Holmes KV, et al. Family coronaviridae. *Virus Taxon* 2012; 806–28.
3. Neuman BW, Adair BD, Yoshioka C, Quispe JD, Orca G, Kuhn P, et al. Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy. *J Virol* 2006;80:7918–28.
4. Lai MM, Cavanagh D. The molecular biology of coronaviruses. *Adv Virus Res* 1997;48:1–100.
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
6. Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:934–43.
7. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20.
8. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683–90.
9. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr* 2020;9:51.
10. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020;395:809–15.
11. Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. *Lancet* 2020;395: 1741–3.
12. Zhang G, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. *Respir Res* 2020;21:74.
13. Bansal M. Cardiovascular disease and COVID-19. *Diabetes, Metab Syndrome: Clin Res Rev* 2020;14:247–50.
14. Gallagher PE, Ferrario CM, Tallant EA. Regulation of ACE2 in cardiac myocytes and fibroblasts. *Am J Physiol Heart Circ Physiol* 2008;295:H2373–9.
15. Alenina N, Xu P, Rentzsch B, Patkin EL, Bader M. Genetically altered animal models for Mas and angiotensin-(1–7). *Exp Physiol* 2008;93:528–37.
16. 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.
17. Rico-Mesa JS, White A, Anderson AS. Outcomes in patients with COVID-19 infection taking ACEI/ARB. *Curr Cardiol Rep* 2020;22:1–4.
18. Johnson RM, Vinetz JM. Dexamethasone in the management of covid-19. *BMJ* 2020;370:m2648.
19. Crosby JC, Heimann MA, Bureson SL, Anzalone BC, Swanson JF, Wallace DW, et al. COVID-19: a review of therapeutics under investigation. *J Am Coll Emerg Physicians Open* 2020;1:231–37.
20. Phelamei S. COVID-19 vaccine development status: CureVac results in 2 months; sixth Chinese jab begins human trials. Available from: <https://www.timesnownews.com/health/article/moderna-or-oxford-who-is-leading-the-world-in-covid-19-vaccine-race/608690> [accessed 24 July 2020].