COVID-19 and Its Role In Myocarditis and An Exercising Heart

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Abstract

Up until this point, not much is known about the impact the SARS-CoV-2 virus has on the heart. At the beginning of the pandemic in March, 2020, COVID-19 was known for causing pneumonia and various other complications stemming from lung damage. Recent research has hypothesized the possible effect COVID-19 can have on other body systems, including the heart. A recent observational study in Germany found that out of 100 athletes, recently recovered from COVID-19, 78 had abnormal findings on CMR imaging studies. One possible link between the heart and COVID-19 is myocarditis, or inflammation of the heart due to viral infection. The importance of this review lies within the fact myocarditis is the cause of 7% to 20% of sudden cardiac death in young athletes. This review will discuss the research on the pathology of the potential link between COVID-19 and the heart (specifically myocarditis), the prevalence of heart injury and COVID-19, and the steps recreational and professional athletes should consider taking before return to action.

Introduction

COVID-19 has been a public health concern since early 2020. Labeled as a pandemic in March of 2020, the initial health concerns associated with the virus was pneumonia and the "ground glass" appearance on a chest X-ray. However, there is an increase in research that finds a more systemic effect of the SARS-CoV-2 virus; one such example is the potential for cardiac damage. Although not much research has been provided in this area, there is a sufficient amount of information to link these two problems together. This paper will review the present research on the link between COVID-19 and cardiac damage, with a focus on how exercise may or may not exacerbate this damage. It will also take a look at the impact exercise has and whether it can potentially mitigate or exacerbate the potential cardiac damage associated with COVID-19. This

review provides a stepping point into further investigation to find a connection between COVID-19 and long-term cardiac injury.

Background

In December 2019, a respiratory disease, known as COVID-19, was caused by a coronavirus and started to spread in areas of Wuhan, China. Since then, it has spread rapidly around the world and on March 11, 2020, the World Health Organization declared COVID-19 a pandemic. According to the CDC, in the United States alone, there have been over 500,000 deaths caused by this virus. The virus causing COVID-19 is referred to as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) due to its high relation to the SARS-CoV outbreak from 2002-2003 (1). The life cycle of the virus with the host consists of 5 steps: attachment, penetration, biosynthesis, maturation, and release (1). The virus itself consists of five proteins, one of high importance is the spike protein. The spike protein is known to bind to the angiotensin converting enzyme 2 receptor and this is how it gains entrance into the human body. ACE2 receptors are predominantly expressed on epithelial cells of the lung allowing the virus to enter and destroy these cells, with main symptoms being fever and cough, and the most frequent manifestation of the disease being pneumonia (2). However, not much is known regarding the virus binding to other ACE2 receptors in the body. For example, ACE2 receptors expression is high in the heart, ileum, kidney, and bladder as well (1). According to an observational study done by University Hospital Frankfurt in Frankfurt, Germany, in which 100 participants who recently recovered from COVID-19, 78 out of 100 patients had some form of abnormal finding on cardiovascular magnetic resonance (CMR) imaging.

Cardiac injury prevalence with COVID-19

Like previously mentioned, the study done by University Hospital Frankfurt showed abnormal CMR findings in 78 out of 100 monitored patients. CMR imaging was performed, on average, 71 days post-COVID-19 diagnosis and along with abnormal imaging studies, 71 patients had abnormal troponin levels (greater than 3pg/mL) and 5 patients had significantly elevated troponin levels (greater than 13.9pg/mL) (3). It is also important to note that of the 100 patients observed, 67 patients recovered at home while only 33 required hospitalization. The most prevalent abnormality was the finding of myocarditis in 60 patients, regardless of pre-existing conditions or severity of COVID-19 infection (3). In this study, myocarditis can be defined by abnormal levels of native T1 and T2 to rule out potential influence from preexisting conditions. T1 and T2 mapping is a technique integrated during a CMR study to assess for potential heart damage. Specifically, T2 is used in finding myocardial edema in patients with acute myocardial infarction, myocarditis, stress cardiomyopathy, sarcoidosis, and cardiac allograft rejection (4). One more study found SARS-CoV-2 virus located in the myocardium in 24 of 39 autopsies reviewed (5). Another study examined a cohort of hospitalized patients in China and compared the prevalence of elevated troponin levels in COVID-19 patients. It was found that around 7% to 17% of patients diagnosed with COVID-19 had elevated troponin levels and this incidence was increased with the severity of the disease, 22% of patients in the ICU and 59% of patients who died from the disease (6). It is important to note that cardiac involvement refers not only to myocarditis, abnormal T1 and T2 levels, but also acute cardiac injury and elevated troponin levels. Some other significant cardiac complications include biventricular heart failure, arrhythmias, and occasionally cardiogenic shock and death. Finally, a study compared cardiac magnetic resonance imaging of 26 college athletes from different sports (football, soccer, track basketball, and lacrosse) who recently recovered from

COVID-19 and found that four athletes exhibited signs of myocarditis (7). Important things to take into account is that none of the athletes required hospitalization for symptoms, and of the four athletes with myocarditis findings in the CMR images, only two of them reported experiencing any symptoms at all. This shows a large correlation of cardiac involvement with COVID-19, however, there needs to be more research done to explore the exact mechanism of how the virus can damage the heart.

COVID-19 Pathology and the Impact on the Heart

The numerous studies reviewed above have provided countless examples of a large quantity of individuals suffering from heart damage post-COVID-19 infection. The pathway for how the virus can infect the heart has not been fully understood, but there have been various possible mechanisms of action proposed. For individuals with preexisting conditions (age, hypertension, cardiovascular disease, etc), it has been suggested that these conditions lead to increased expression of ACE2, which will lead to increased susceptibility from the SARS-CoV-2 virus (3). As previously mentioned, it is reported that the SARS-CoV-2 virus can enter the body by the virus spike proteins binding to the ACE2 (angiotensin converting enzyme-2) receptors located throughout the body, mostly located in the heart and lungs. An experiment from Bermejo et al. reviewed the impact the SARS-CoV-2 virus has on cardiac tissue derived from human induced pluripotent stem cells (iPSCs) via *ex vivo* experiments. The study revealed “robust transcriptomic and morphological signatures of damage in cardiomyocytes” (8). The morphological changes included distinct sarcomere fragmentation, specifically cleavage of thick filaments, and various cardiomyocytes lacking nuclear DNA. Interestingly, the study also reviewed human autopsy reports from individuals diagnosed with COVID-19 and myocarditis and there were similar findings, such as sarcomere damage and cardiomyocytes without a nucleus. To

find a possible mechanism leading to damage of these cells, the study tested three main types of iPSC cardiac cells: cardiomyocytes, cardiac fibroblasts, and endothelial cells. Interestingly, the sarcomere damage and a lack of a nucleus was only found in the cardiomyocytes, but not the cardiac fibroblasts or endothelial cells. Also specific to the cardiomyocytes, it was found that SARS-CoV-2 infection led to dysregulation of the contractile machinery of these cells. What makes this so interesting is the fact that ACE2 receptors can be found only in cardiomyocytes, but not the other two cell types. The study furthered this investigation by using ACE2 inhibitors before infection with SARS-CoV-2 which resulted in less viral positive results compared to wild-type cells. Other proposed mechanisms include the idea myocarditis is caused by a cytokine storm triggered by the imbalance response from type 1 and 2 T helper cells; also, respiratory dysfunction and hypoxic stress due to lung damage, microvascular thrombosis (blood clots in small blood vessels), and/or systemic response due to the overall infection from COVID-19 resulting in damage to the cells of the heart.

Myocarditis In An Exercising Heart

In a time where all athletes, recreational or professional, are at risk of contracting the disease, it is important to know the potential effects exercising can have on athletes. The concern is that COVID-19 is not only damaging to the lungs for those infected, but also other body systems, most notably the cardiovascular system. The specific type of cardiac injury reviewed will be myocarditis, or inflammation of the heart. According to the International Society and Federation of Cardiology, myocarditis can be defined as an inflammatory disease of the heart muscle cells and can be pathologically identified by histology and immunohistochemical techniques as an infiltration of mononucleated cells in the myocardium. The importance regarding myocarditis in athletes is that previous studies have shown that myocarditis accounted for 7% to 20% of sudden

cardiac death in young athletes (9). Myocarditis can be characterized into three different phases: an early acute phase, a sub-acute phase, and a chronic phase. In the early acute phase, viral replication is occurring within the myocytes. During the sub-acute phase, the body's natural immune system is responding to the virus. And lastly, the chronic phase can range from complete recovery from infection to cardiac failure. There has been little research on the impact exercise can have during the acute phase of an infection. However, one study has shown that exercise can actually accelerate viral replication, a heightened inflammatory response leading to cell necrosis, and a proarrhythmic unstable myocardial substrate. In this study, experimenters infected mice with Coxsackievirus B3, which causes myocarditis. The mice were separated into four groups: infected-exercised, infected-unexercised, uninfected-exercised, and uninfected-unexercised. Exercise was simulated by having the mice swimming for 60 minutes. Results, along with those previously mentioned, include increased myocardial viral titers three days after infection which significantly increased with exercise and increased mortality (20% to 30%) with exercise (10).

Exercise to improve the immune system

The previous discussion involved how exercise can damage cardiac cells and be a potential risk of worsening infection However, it is widely known that exercise is beneficial for individuals. Exercise promotes a healthy lifestyle, healthy choices, and improves long-term health. Unfortunately, during an infection, exercise can seem like a poor decision, however, there are studies providing support that exercise can strengthen the immune system and help battle the infection(s) present in the body, including COVID-19. Taking a group of participants in a college badminton club (regular exercise two to three times a week) and a group of healthy college individuals living a more sedentary lifestyle, researchers compared cytokine production and other innate defense molecules after microbial and non-microbial stimulation (11). At baseline, there

was no significant difference between the two groups in cytokine levels. However, without any stimulation, toll-like receptors (TLRs) expression was significantly increased in the regular exercise group. More specifically, TLR2 and TLR7 were the TLRs examined for this study. TLRs are known to aid in the innate immune response. Upon activation of TLRs via pathogen-associated molecular patterns (PAMPs), TLRs will initiate the innate immune response and aid in creating inflammatory cytokines, interferons, and other mediators of the immune system. The next step was to measure the expression of these receptors after viral and bacterial stimulation. The study revealed that the regular exercise group had significantly higher levels of TLR2 and TLR7 expression compared to the sedentary group after viral stimulation (with hepatitis B core antigen). In its relation to SARS-CoV-2, toll-like receptors are thought to be involved in the failure of initial clearance and subsequent development of COVID-19 (12). The virus itself may prevent an accurate and effective immune response by inhibiting the tumor necrosis factor (TNF)-receptor-associated-factors, which induce interferon regulatory factors (INFs) upon activation from TLR7. Furthermore, an agonist of TLR7 may prevent severe symptoms of COVID-19 and work with antiviral therapy (12). As previously mentioned, the SARS-CoV-2 virus depends on the ACE2 receptor to enter the body, and ACE2 is part of a larger system called the renin angiotensin system (RAS). The RAS system can be divided into to axes: ACE, angiotensin II and AT1 receptor (ACE/AngII/AT1R axis) and the ACE2, angiotensin 1-7 (1-7), and the Mas receptor (ACE2/Ang1-7/Mas axis) (13). The two axes can be thought of as competing against one another in terms of their effects on the body. The ACE/Ang II/AT1R axis is associated with vasoconstriction, cell proliferation, organ hypertrophy, and sodium retention; overactivation of this axis is seen in diseases such as obesity, DM, and CVD causing inflammation. The ACE2/Ang1-7/Mas axis causes an anti-inflammatory, vasodilator, antiproliferative, cardioprotective, and renoprotective

response in the body. During COVID-19 infection, it has been shown that the virus will reduce the expression of ACE2 receptors, and therefore causing an imbalance between the two axes, and more so an overexpression of the inflammatory response of the ACE/AngII/AT1R axis. Given this information, many therapeutic options for COVID-19 have looked at a mechanism of increasing the ACE2 receptor and/or inhibiting the AngII axis. One such therapeutic option is an increase in physical exercise. Physical exercise has been shown to downregulate ACE/AngII/AT1R axis, upregulate ACE2/Ang1-7/Mas axis, and actually shift the RAS system toward the ACE2/Ang1-7/Mas axis (13).

Discussion

The research on how COVID-19 and its impact on the heart is limited but emerging. With this virus being an ongoing issue in the world, it is important to know the potential future impact and not just the problems associated with the initial infection. One of the most important findings in this review was the study that revealed COVID-19 infection can cause damage to the myocardiocytes, including enucleated cells and damage to the contractile fibers of the human heart. A few important questions that should be considered is how to get back to exercising? How can athletes return to the field/court/ice after being diagnosed with COVID-19? When should athletes be allowed to return to action? How do we know when is the best time to return to action? Would certain exercises during a COVID-19 infection have a more negative impact on overall health compared with others? For example, taking a look at return protocols for National Football League (NFL) players have raised some concerns. According to the NFL, if an athlete tests positive and is asymptomatic he can return once ten days have passed since the initial positive test or five days have passed since the initial positive test with two consecutive negative PCR virus tests 24-hours apart within the five-day period. There is a different protocol for athletes testing positive and

showing symptoms, and this includes a rule of ten days after the initial symptoms first appeared and three days since last experiencing symptoms. Along with the NFL, there are many other recommendations that a person can return to regular exercise around ten days after symptoms resolve (14). The problem is that it has been shown that damage can occur in those experiencing symptoms, and those who do not. The research presented in this article determined that damage to the heart can occur upon initial infection in the myocardiocytes and, in some cases, can be seen postmortem. Common suggestions of returning to exercising include "seven days after symptoms have stopped at 50%" (2). The question posed would be, is this really enough time to recover given the potential long-term damage? It is also worth mentioning the number of medical professionals surrounded by these athletes and how constant testing measures are taken to ensure the safety of these athletes. However, what about the recreational athlete? Those who exercise for fun, and those who exercise to stay in shape. It is safe to assume that most professional athletes are in great physical shape and there are no worries for pre-existing conditions so the long-term prognosis for these athletes would usually be favorable. Certain conditions like hypertension, CVD, hyperlipidemia, etc are at a high prevalence in this country; in fact, according to the CDC, almost half (48%) of the U.S. population has been diagnosed with hypertension. Individuals with these pre-existing conditions are obviously at a higher risk of cardiac damage and with the potential of exercise adding to this risk, it is important to continue to research how these individuals can return. One effective step is screening these individuals and making sure it is safe to return. One article by Phelan et al discusses the potential steps individuals can take to ensure the safety of returning to sport. Some proposed screening methods like an electrocardiogram (ECG), troponin testing, and cardiovascular magnetic resonance imaging (CMR) have their limitations. In ECGs, there is not enough evidence in diagnosing myocarditis from an ECG as they are used for more acute problems

leading to sudden cardiac death. Troponin testing may not be the most effective method as this review has shown a wide range of abnormal troponin levels in COVID-19 patients, and studies have shown that competitive athletes can have altered troponin levels up to 48 hours after exercise (16). CMR imaging has been shown to be the most effective form of diagnosing myocarditis and is widely considered "the gold standard." One effective way of diagnosing myocarditis was with the use of abnormal T1 and T2 levels. However, it has been reported that CMR imaging is unable to find the prolonged prognosis of the abnormalities found in the images. After screening and possibly finding cardiac involvement, how should athletes and non-athletes return to exercise. One possible solution is the use of resistance training. Resistance training has been an essential part of physical rehab programs as the exercise has a long list of benefits and can be performed by a wide range of athletes/individuals. Along with strength improvement, benefits include blood pressure control, improved bone mineral density, and glucose & weight management (17). Another benefit to resistance training (RT) is the lack of strain on the cardiorespiratory system on individuals when compared with aerobic exercises. With COVID-19 already adding stress to the respiratory system and potentially cardiac system, it would be best to eliminate any added stress. When considering the "open window theory," the theory that there is a state of immunosuppression after prolonged high-intensity exercise (18), it would be important to stress the importance of returning to exercise at a minimal intensity. However, this is just a theory and more research is needed to provide answers on how intensity of exercise can impact patients with COVID-19. Overall, more research is needed for the topics of COVID-19 and its effect on the heart, along with COVID-19 and exercise. The studies presented in this paper showed the potential benefits and risks of exercise with COVID-19. The information provided provides a strong argument that there definitely could be some form of involvement of the cardiac system with the SARS-CoV-2 virus. With the large

number of individuals with pre-existing conditions involving the heart and the lasting impact of COVID-19, this research is important to continue and hopefully find more answers on the lasting impact of the virus. The link between COVID-19 and the heart has been widely unknown since the spread of the virus. However, significant research findings including the prevalence of cardiac injury after COVID-19 infection and research finding damage to cardiomyocytes (enucleated cells, damaged contractile fibers, and sarcomere fragmentation) provides sufficient evidence for this link.

Works Cited

1) Driggin, Elissa, et al. “Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic.” *Journal of the American College of Cardiology*, By the American College of Cardiology Foundation. Published by Elsevier., 12 May 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7198856/.

2) Emery , Michael, et al. “Exercise and Athletics in the COVID-19 Pandemic Era.” *American College of Cardiology*, May 2020, www.acc.org/Latest-in-Cardiology/Articles/2020/05/13/12/53/Exercise-and-Athletics-in-the-COVID-19-Pandemic-Era.

3) Valentina O. Puntmann, MD. “Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From COVID-19.” *JAMA Cardiology*, JAMA Network, 1 Nov. 2020, jamanetwork.com/journals/jamacardiology/fullarticle/2768916?guestAccessKey=698ebd4c-5c29-4069-9ef6-8839bcbc07de&utm_source=For_The_Media&utm_medium=referral&utm_campaign=ftm_links&utm_content=tfl&utm_term=072720.

4) Zoppi, Lois. “Myocardial T1 and T2 Mapping.” *News*, 24 Jan. 2019, www.news-medical.net/health/Myocardial-T1-and-T2-Mapping.aspx.

5) Lindner, Diana, et al. “Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases.” *JAMA Cardiology*, U.S. National Library of Medicine, Nov. 2020, pubmed.ncbi.nlm.nih.gov/32730555/.

6) Shaobo Shi, MD. “Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China.” *JAMA Cardiology*, JAMA Network, 1 July 2020, jamanetwork.com/journals/jamacardiology/article-abstract/2763524.

7) Rajpal, Saurabh, et al. “Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection.” *JAMA Cardiology*, JAMA Network, 1 Jan. 2021, jamanetwork.com/journals/jamacardiology/fullarticle/2770645.

8) Pérez-Bermejo, Juan A., et al. “SARS-CoV-2 Infection of Human IPSC-Derived Cardiac Cells Predicts Novel Cytopathic Features in Hearts of COVID-19 Patients.” *BioRxiv*, Cold Spring Harbor Laboratory, 1 Jan. 2020, www.biorxiv.org/content/10.1101/2020.08.25.265561v1.full.

9) Metzl, Jordan D., et al. “Considerations for Return to Exercise Following Mild-to-Moderate COVID-19 in the Recreational Athlete.” *HSS Journal ®*, Springer US, 10 Aug. 2020, link.springer.com/article/10.1007/s11420-020-09777-1.

10) Kiel, R. J., et al. “Coxsackievirus B3 Myocarditis in C3H/HeJ Mice: Description of an Inbred Model and the Effect of Exercise on Virulence.” *European Journal of Epidemiology*, Kluwer Academic Publishers, Sept. 1989, link.springer.com/article/10.1007/BF00144836.

11) Zheng, Qishi, et al. “Regular Exercise Enhances the Immune Response Against Microbial Antigens Through Up-Regulation of Toll-like Receptor Signaling Pathways.” *Cellular Physiology and Biochemistry*, Karger Publishers, 11 Sept. 2015, www.karger.com/Article/FullText/430391.

12) Onofrio, Livia, et al. “Toll-like Receptors and COVID-19: a Two-Faced Story with an Exciting Ending.” *Future Science* , July 2020, www.future-science.com/doi/pdf/10.2144/fsoa-2020-0091.

13) Evangelista, Fabiana S. “Physical Exercise and the Renin Angiotensin System: Prospects in the COVID-19.” *Frontiers in Physiology*, Frontiers Media S.A., 15 Oct. 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7593780/.

14) Kim, Jonathan, et al. “Coronavirus Disease 2019 and the Athletic Heart.” *JAMA Cardiology*, JAMA Network, 1 Feb. 2021, jamanetwork.com/journals/jamacardiology/fullarticle/2772399.

15) Phelan, Dermot, et al. “Screening of Potential Cardiac Involvement in Competitive Athletes Recovering From COVID-19: An Expert Consensus Statement.” *JACC. Cardiovascular Imaging*, By the American College of Cardiology Foundation. Published by Elsevier., Dec. 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7598679/.

16) Zheng, Ying-Ying, et al. “COVID-19 and the Cardiovascular System.” *Nature Reviews. Cardiology*, Nature Publishing Group UK, May 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7095524/.

17) Gentil, Paulo, et al. “Resistance Training Safety during and after the SARS-Cov-2 Outbreak: Practical Recommendations.” *BioMed Research International*, Hindawi, 23 Sept. 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7532374/.

18) Ferreira-Júnior, João B., et al. “Exercise: A Protective Measure or an ‘Open Window’ for COVID-19? A Mini Review.” *Frontiers*, Frontiers, 29 Apr. 2020, www.frontiersin.org/articles/10.3389/fspor.2020.00061/full.

19) Yuki, Koichi, et al. “COVID-19 Pathophysiology: A Review.” *Clinical Immunology (Orlando, Fla.)*, Elsevier Inc., June 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7169933/.