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FINAL THESIS

Myocardial Structural Changes in Patients after COVID-19 Disease: Case Description and Literature Evaluation

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I. Abbreviations

Abbreviation	Definition
ACE2	Angiotensin converting enzyme 2
ACS	Acute coronary syndrome
ADAM-17	Metalloproteinase domain 17
AM	Acute myocarditis
ARB	Angiotensin receptor blockers
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
CMR	Cardiac magnetic resonance
CVD	Cardiovascular disease
DCM	Dilated cardiomyopathy
DM	Diabetes Mellitus
ECG	Electrocardiogram
EF	Ejection fraction
GLS	Global longitudinal strain
HF	Heart failure
IL	Interleukin
IV	Intravenous
LGE	Late-gadolinium enhancement
LLC	Lake Louise Criteria
LV	Left ventricle
LWMH	low-molecular-weight heparin
PCI	Percutaneous coronary intervention
RAAS	Renin–angiotensin–aldosterone system
RNA	Ribonucleic Acid
RV	Right ventricle
STEMI	ST-segment elevation myocardial infarction
TMPSSR2	Transmembrane protease serine 2
TNF	Tumor necrosis factor
TTE	Trans-thoracic echocardiography
UFH	Unfractioned heparin
VTE	Venous thromboembolism

II. Summary

Based on the studies reviewed in this thesis, COVID-19 is associated with cardiovascular diseases as well as structural alterations of the myocardium, both through direct cardiac injury and indirectly through affecting multiple organ systems, which may worsen underlying cardiac diseases or even cause cardiovascular diseases through vascular dysfunction or inflammation. COVID-19 disease has been associated with coagulation abnormalities both clinically and histopathologically, and evidence suggests vascular inflammation and endothelial dysfunction could occur due to COVID-19 infection. Importantly, the major pathophysiological trigger for organ dysfunction, including cardiovascular manifestations, is an imbalanced immune system response. Myocardial injury in association with COVID-19 has been recognized as a significant predictor of mortality in patients. This highlights the importance of establishing prognostic markers and novel treatments to decrease the incidence of myocardial injury. In addition, the downregulation of the Angiotensin-converting enzyme 2 (ACE2) receptor as a defense mechanism and consequent unwanted downregulation of myocardial protective effects provides an interesting topic for further research as a possible therapeutic target or a marker of complications. However, it seems that while initially COVID-19-myocarditis was reported fairly frequently, the prevalence of myocarditis fulfilling diagnostic criteria is rare, while inflammation of the myocardium on imaging and histopathology is more common. As myocardial inflammation without myocarditis has been reported in imaging and histopathological studies consistently, more research is required to assess its effect on developing cardiac comorbidities in the future. Other structural alterations such as hypertrophy and fibrosis of the myocardium have been reported on autopsies and imaging, but to determine whether they are directly due to COVID-19 infection, or due to underlying cardiac pathology, is still undetermined. Further research is required to determine the causality between COVID-19 and the aforementioned structural changes in the myocardium. Long-term studies on the relationship between COVID-19 and the risk of developing cardiovascular diseases after initial infection are limited, but recent studies with relatively large patient cohorts have been able to demonstrate an increased 12-month risk of cardiovascular disease, even in patients without prior known comorbidities.

III. Clinical case

A case report of a 31-year-old, previously healthy woman is presented. The patient gave birth in March of 2022 (first pregnancy, vacuum-assisted successful vaginal delivery at 39 weeks + 5 days). Pregnancy was complicated by gestational diabetes, gestational hypertension with mild-moderate preeclampsia, and thrombocytopenia (63 x109/l of platelets). During pregnancy patient was taking methyldopa 250 mg 3 times a day due to gestation hypertension, diabetes was treated only with diet. Pregnancy (at the end of 3rd trimester) was complicated by COVID-19 infection. No echocardiograms (ECG) were recorded during pregnancy, but postpartum ECG showed deep negative T wave inversions, and the patient was referred to a cardiologist. Cardiac ultrasound showed an ejection fraction (EF) of around 50%, with insufficient data for diagnosis of peripartum cardiomyopathy.

One year after delivery due to dyspnoea during physical exercise patients underwent repeatedly outpatient cardiological consultation. Objectively patient had a normal body structure (BMI 23 kg/m2), heart rate was regular at 86 bpm, blood pressure (BP) of 140/93 mmHg, had no signs of cardiac decompensation. ECG revealed sinus rhythm, 88 bpm, up to 0.5 mm ST segment depressions with negative T waves in leads II, III, AVF, and up to 1 mm ST segment depressions in leads V3-V6 with biphasic T waves in leads V3-V6 (**Figure 1**). Blood examination at that time revealed nonelevated Troponin I (2 ng/l) and BNP (13.7 ng/l) concentrations. Transthoracic echocardiography showed normal diameters of all cardiac chambers, without significant valvular heart diseases, and normal systolic and diastolic function of the left ventricle. Ambulatory BP monitoring showed normotension without any antihypertensive medications during the day (average BP 114/77 mmHg) and night time (average BP 110/71 mmHg). 24-hour ECG monitoring was performed, which showed sinus rhythm from 53 to 120 bpm (average heart rate 77 bpm), without any arrhythmia or conduction disturbances, and with permanently negative T waves. A bicycle exercise test was negative with hyperkinetic reaction to physical exercise and without significant dynamics of ST segment and T waves. Additionally, no rhythm disturbances were registered during the bicycle exercise test. In 6 months, the patient underwent coronary artery computed tomography angiography, which showed normal coronary arteries without any calcinosis or noncalcified plaques, without anomalies but with hypoplastic right coronary artery (**Figure 2**). Consequently, cardiac magnetic resonance tomography (CMR) was performed, which demonstrated mild dilation of the left ventricle with a small amount of fluid in the pericardium (separation of pericardial layers up to 6 mm) (**Figure 3, panels A and B**). On late CMR gadolinium enhancement sequence, a small confluent fibrotic foci were visible in the inferior, inferoseptal, and partially lateral walls of the left ventricle with non-ischaemic distribution in midmyocardium and subepicardium (**Figure 3, Panels C-E**). By the CMR Lake Louise criteria [1], a diagnosis of probable COVID-19 myocarditis at the end of pregnancy was established. An endomyocardial biopsy was not performed, so a definitive diagnosis was not made. As the patient had no symptoms at this time, cardiac biomarkers and 24-hour ECG monitoring were normal, no treatment was initiated and a follow-up cardiologist`s consultation was prescribed in 12 months or before conception.

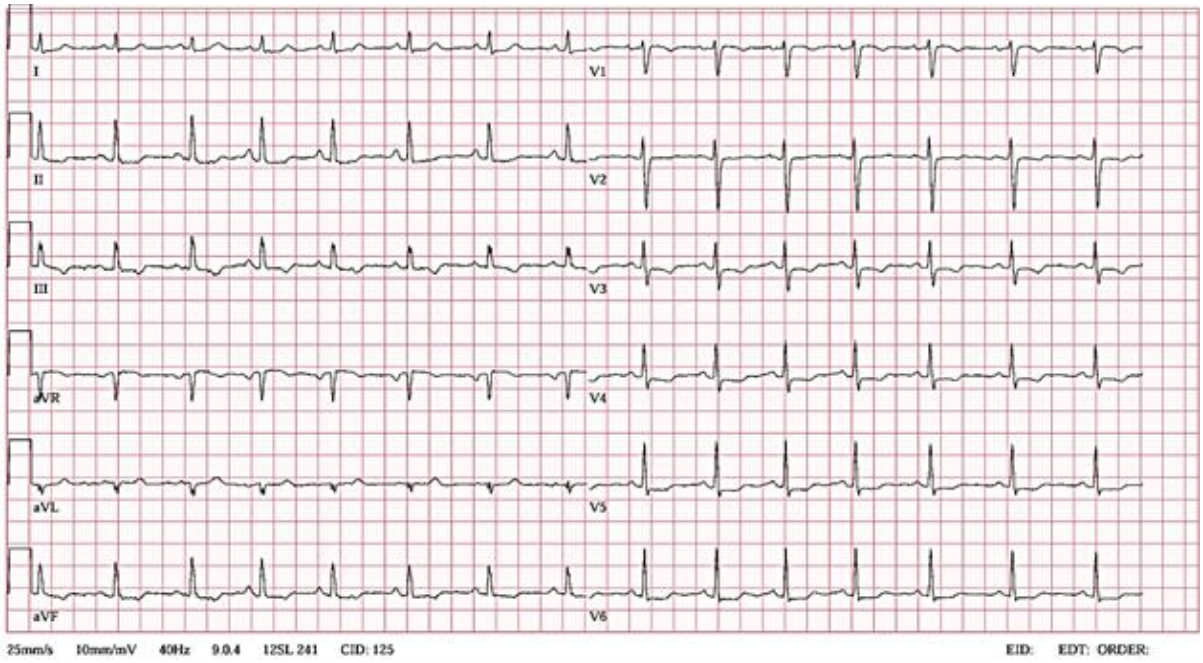

Figure 1. Electrocardiogram. Sinus rhythm, 88 bpm, up to 0.5 mm ST segment depressions with negative T waves in leds II, III, AVF and up to 1 mm ST segment depressions in leads V3-V6 with biph asic T waves in leads V3-V6.

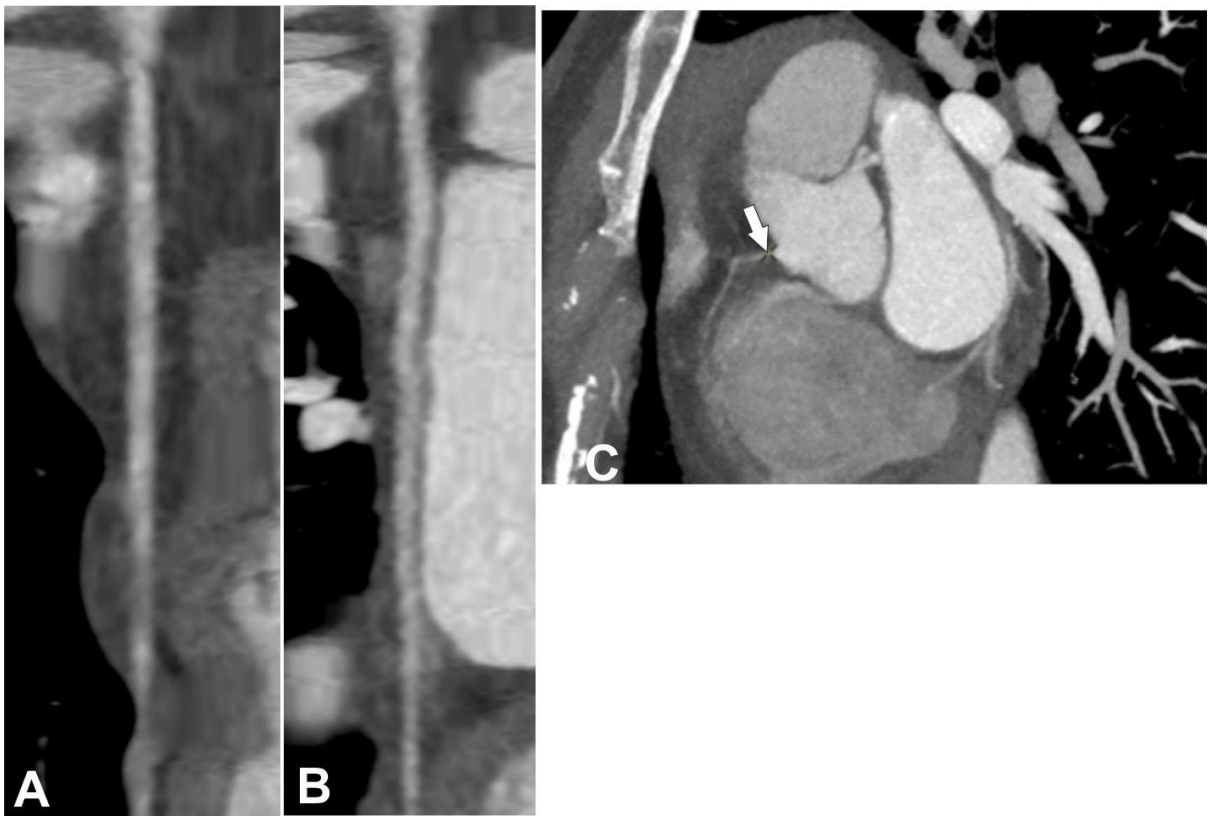

Figure 2. Coronary artery computed tomography angiography images. Curved multiplanar reformations along the vessel center line of left anterior descending artery (A), left circumflex artery (B) and hypoplastic right coronary artery (depicted with arrow, C).

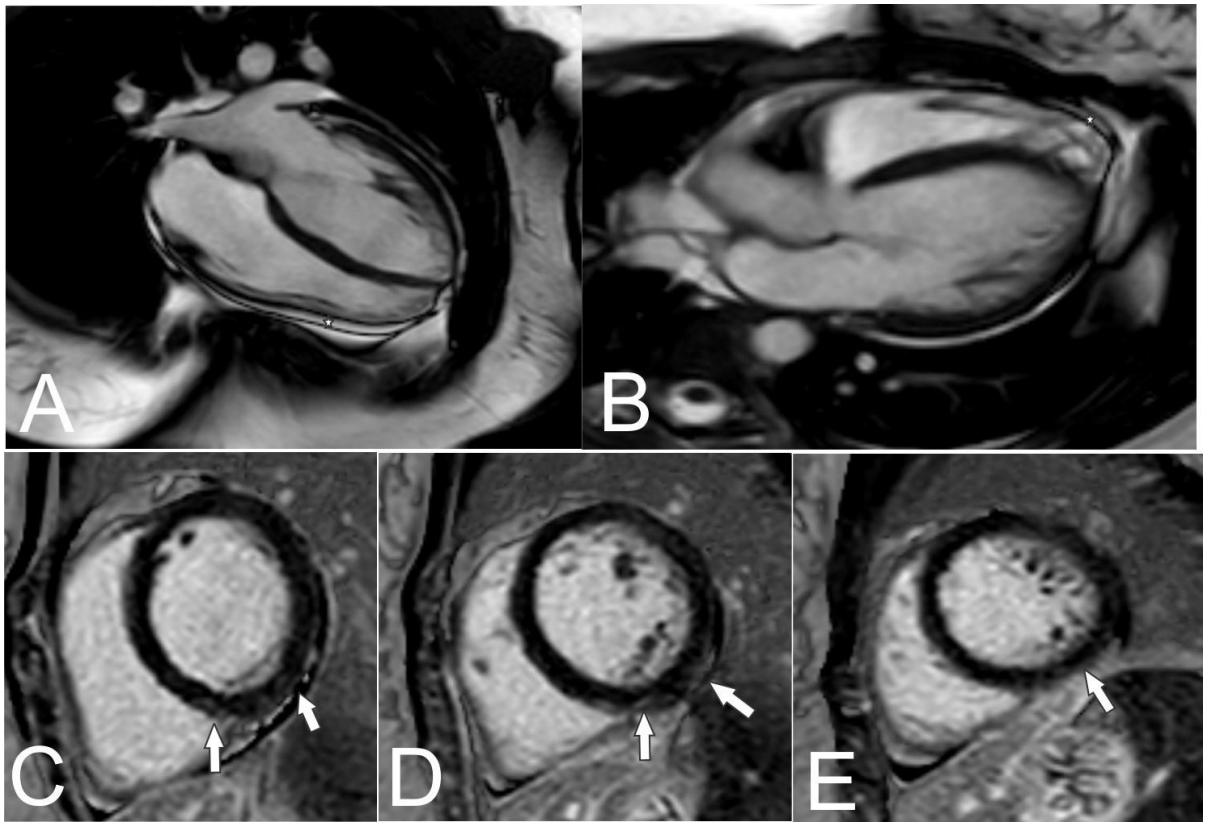

Figure 3. CMR images. A, 4 chamber heart view (cine image, separation of pericardial layers is depicted with asterisk). B, 3 chamber heart view (cine image, separation of pericardial layers is depicted with asterisk). C-E, late gadolinium enhancement short axis images at basal (panel C), midventricular (panel D) and apical (panel E) segments (arrows depict midmyocardial and subepicardial late gadolinium enhancement (fibrotic) foci.

IV. Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has affected hundreds of millions of people worldwide since its beginning in the early part of 2020. It has had an unprecedented impact on individual health, as well as healthcare practices and the economic situation throughout the world. Cardiovascular implications of COVID-19 were quickly discovered, as reports of cardiac symptoms such as chest pain and arrhythmias, as well as reports of coagulation abnormalities and myocarditis-like infections were plentiful early on during the pandemic. The myocardium, the middle layer of the heart, is the muscle that facilitates the contraction and relaxation of the heart walls to receive and pump blood into the systemic circulation. As reports of cardiovascular diseases in association with COVID-19 infection started circling, while simultaneously it was discovered that SARS-CoV-2 gains entry into the host cells through the binding of its spike protein to the angiotensin-converting enzyme 2, which is expressed in the heart and the vascular system, increasing interest towards COVID-19`s cardiovascular effects began. Due to the recent occurrence of the pandemic, limited data is available on large patient cohorts, where underlying cardiac diseases have been taken into consideration when assessing the cardiovascular effects of COVID-19. Furthermore, follow-up studies in quantifying the long-term risks associated with cardiovascular manifestations of COVID-19 have been scarce, and more research is needed to accurately assess the situation. This thesis aims to summarize the relevant published literature, with a focus on the effects of COVID-19 infection on the myocardial structure and its implications. Furthermore, an overview is provided of the common cardiovascular manifestations, their pathogenesis, mechanism of injury, imaging and histological evidence of myocardial structure alterations, current treatment guidelines, as well as the long-term consequences and risks of cardiovascular disease. Additionally, the representative case of a patient with COVID-19-related myocarditis has been presented.

V. Methodology

5.1. Search Strategy

Google Scholar and PubMed were used for in the literature search. Keywords such as "myocardium and Covid 19", "Covid 19 and the cardiovascular system", "cardiac pathology in Covid 19", "cardiac structure alterations", "effects of Covid 19 on the myocardium" and "organ dysfunction and Covid 19" were used to search for the relevant literature.

5.2. Selection Criteria

Sources were evaluated according multiple criteria. First, the source had to be in line with the purpose of the literature review. Second, the source had to be the primary source. Third, the sources had to be as recent as possible. The topic of the literature review is very new, so none of the sources date back to more than 2020. When presenting information in this literature as the current understanding of the topic, relevant information from publications starting from 2022 onwards has been collected, since in the beginning of the pandemic a lot of the studies done were still done on very small sample sizes and in a short time frame. Additionally, internationally recognized guideline, especially when talking about the current approaches to treatment and management, has been taken into account.

VI. Background

6.1. COVID-19 disease

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also referred to as COVID-19, was declared a pandemic by the World Health Organization in March 2020. The manifestations of COVID-19 are variable and they range from asymptomatic infection to a multi-organ failure and death. Pulmonary involvement is the most common and dominant manifestation of COVID-19. SARS-CoV-2 frequently causes a pulmonary infection manifesting in a range of clinical presentations, from asymptomatic subclinical infection to severe viral pneumonia, acute respiratory distress syndrome (ARDS), a life-threatening respiratory failure requiring mechanical ventilation and admission to the intensive care unit, as well as septic shock and single or multiple organ dysfunction. In addition, an uncontrolled and imbalanced response from the host to SARS-CoV-2 infection can trigger a "cytokine storm" resulting in multi-organ failure, while coagulation abnormalities have been reported in patients with COVID-19 leading to thromboembolic complications.

In addition to acute illness, a syndrome known as long-COVID has emerged. It is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation. Commonly reported symptoms include fatigue and "brain fog". Additional symptoms include insomnia, changes in smell and taste, shortness of breath, chest pain, palpitations, dizziness, depression, and anxiety. In some cases, the symptoms are disabling, preventing patients from working or even continuing their normal daily activities.

6.2. Cardiovascular implications in COVID-19 patients

Numerous cardiovascular complications such as acute myocardial injury, acute heart failure, pulmonary embolisms, arrhythmias, acute coronary syndrome, myocarditis, and pericardial effusion have been reported in patients infected with SARS-CoV-2. Because 1 or more of these etiologies may present simultaneously, it can sometimes be a challenge to identify a specific underlying cause. SARS-CoV-2 gains entry into the host cells through the binding of its spike protein to the angiotensin-converting enzyme 2 (ACE2), with assistance from the host transmembrane protease serine 2 (TMPSSR2). Both of these proteins are expressed in the heart too. The associated cardiovascular manifestations of COVID-19 are primarily thought to occur through direct damage to myocardial tissues and an indirect inflammatory storm. Myocardial injury with COVID-19 has been extensively reported, with rates varying depending on the population studied. Early on during the pandemic, myocardial injury caused by COVID-19 was reported only in hospitalized patients. However, cardiac involvement has been found in a proportion of patients recovered from COVID-19. Cardiac magnetic resonance manifestations have been variable, including myocardial edema, fibrosis, and impaired right ventricle function. Similar findings associated with inflammatory infiltrates, and fibrotic and hypertrophic changes have been reported in post-mortem autopsies too. It is unclear whether these reported changes are directly through COVID-19 infection, or due to worsening of underlying cardiovascular comorbidities.

6.3. Normal Myocardial Structure and Function

The myocardium is the middle and thickest layer of the heart wall. This layer lies in between the single-cell endocardium layer, which lines the inner chambers, and the outer epicardium, which is composed of a part of the pericardium that surrounds the heart. On a cellular level, the myocardium is composed of cells called cardiomyocytes. Cardiomyocytes are striated, and branched, contain many mitochondria, and are under involuntary control of the autonomic nervous system. A unique cellular and physiological feature of cardiomyocytes is the intercalated discs, which contain cell adhesions, such as gap junctions. Gap junctions between cardiomyocytes allow for the propagation of coordinated action potentials from one cell to the adjacent cell in a phenomenon known as electrical coupling. These intercalated discs reduce the internal resistance and allow action potentials to spread quickly throughout the entire heart muscle via the passage of charged ions. Therefore, the myocardium is a functional syncytium, with fast synchronized contractions responsible for pumping blood throughout the body. The functional unit of cardiomyocyte contraction is the sarcomere, which consists of thick myosin and thin actin filaments, which slide in between each other to produce contractile force. The sinus node, located within the right atrial myocardium, spontaneously depolarizes due to electrochemical gradient changes and thus determines the heart rate. These depolarizations are currents of ion influx that are carried from the sinus node to the heart muscle via conducting cells. Contraction and relaxation of the myocardium is also dependent on chemical gradients.

The myocardium is responsible for the contractility of the heart and, therefore, the pumping action. The cardiac muscle must contract with enough force and enough blood to supply the metabolic demands of the entire body. This is termed cardiac output and is defined as heart rate x stroke volume, and is determined by the contractile force of the myocardium and the frequency at which it occurs. Under physiological conditions, a change in metabolic demand requires a change in the contractility of the heart [2,3]

The myocardium is supplied by the coronary arteries, drained by the cardiac veins, and innervated by the autonomic nervous system. The sympathetic innervation is via the cardiac fibers from the superior, middle, and inferior cervical ganglion. Sympathetic innervation causes vasodilation of the coronary arteries. The parasympathetic innervation is via the vagus nerve. The vagus nerve will constrict the coronary arteries [4].

Myocardial structural changes have a critical role in cardiovascular function. The myocardium, the muscular tissue of the heart, undergoes structural alterations in response to physiological demands and pathological conditions, as well as aging. These changes can have a significant impact on the heart's function to provide adequate blood flow to itself and the rest of the body`s tissues.

Myocardial hypertrophy refers to the enlargement of cardiac muscle cells. It can occur in response to increased workload due to pathological conditions, such as hypertension or valvular heart disease, or it can be a physiological response to increased workload, such as exercising. While initially compensatory, chronic cardiac hypertrophy can lead to impaired cardiac function and heart failure. This structural change alters the heart's contractile properties and disturbs normal electrical conduction, predisposing individuals to arrhythmias.

Myocardial fibrosis involves the excessive deposition of collagen fibers into the cardiac muscle, leading to increased stiffening of the heart tissue. Fibrosis can result from chronic inflammation, ischemia, or other pathological processes. It reduces the heart's compliance, decreases relaxation, and compromises diastolic function. Additionally, fibrosis disrupts the normal architecture of the myocardium, disrupts normal electrical conduction, and increases the risk of arrhythmias.

Myocardial remodeling encompasses changes in the size, shape, and structure of the heart in response to injury or stress. It can be adaptive, aiming to maintain cardiac output, or maladaptive, playing a part in heart failure progression. Remodeling involves alterations in cardiomyocyte size, extracellular matrix composition, and cardiac chamber geometry. Maladaptive remodeling, characterized by chamber dilation and thinning of the heart walls, weakens cardiac contraction.

Inflammatory processes within the myocardium can lead to structural changes such as edema, cellular infiltration, and tissue damage. Conditions like myocarditis and autoimmune disorders can trigger myocardial inflammation, disrupting normal cardiac function. Chronic inflammation contributes to fibrosis and remodeling, further compromising cardiovascular performance.

6.4. Myocardial pathologies associated with COVID-19 infection

6.4.1. Myocarditis

Acute myocarditis (AM) is an inflammation of the heart of recent onset (less than 1 month). It may be caused by a variety of etiologies, including infections, exposure to drugs or toxins, and abnormal immunoreaction. Its clinical spectrum varies from an asymptomatic or mild illness to severe cardiac conditions with heart failure (HF), refractory arrhythmias, cardiogenic shock, and sudden death. Myocarditis may present in acute, fulminant, subacute, and chronic forms. Acute myocarditis can be defined as a period of <1 month between symptom onset and diagnosis. Fulminant myocarditis is an extremely severe, rapidly evolving form of AM with associated cardiogenic shock requiring interventions such as inotropes or mechanical circulatory support. Subacute myocarditis is characterized by ongoing myocardial damage due to persistent or recurrent myocardial inflammation but can also be defined as healing myocarditis if there is evidence of previous active myocarditis. Additionally, subacute myocarditis can be defined as a period of 1 to 3 months between onset of symptoms and diagnosis. When symptoms continue for a prolonged period, the disease process is considered to be a chronic inflammatory cardiomyopathy. Established histological, immunological, and immunohistochemical criteria, called the Dallas criteria, are currently used to diagnose myocarditis. Based on the Dallas criteria, acute myocarditis is defined as "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical

of the ischemic damage associated with coronary artery disease" [5,6]. The majority of evidence suggests that virus-triggered immune-mediated reactions are the principal cause of cardiomyocyte injury rather than actual direct virus-mediated cell injury. Currently, AM is evolving from being a definitive diagnosis based on histological evidence of inflammatory infiltrates on cardiac tissue via endomyocardial biopsy (EMB), to a working diagnosis supported by high sensitivity troponin increase together with specific cardiac magnetic resonance imaging (CMRI) findings [7]. In patients presenting with mild symptoms and minimal ventricular dysfunction, myocarditis often resolves spontaneously without specific treatment. However, in up to 30% of cases, biopsy-proven myocarditis can progress to dilated cardiomyopathy (DCM) and is associated with a poor prognosis [8].

6.4.2. Fibrosis and Hypertrophy

Cardiac fibrosis is a scarring event in the cardiac muscle that is characterized by an increased collagen type I deposition as well as cardiac fibroblast activation and differentiation into myofibroblasts. These pathological changes can lead to an increase in matrix stiffness and lead to abnormalities in cardiac function. The fibrotic scar lacks contractile capacity, and therefore causes several cardiac dysfunctions, by reducing the ejection fraction (EF), due to the stiffness of the myocardial matrix, or by disrupting electric conductance, leading to arrhythmia. It is important to note however, that while impairing normal cardiovascular function, fibrosis also serves a critical protective role, maintaining the structural integrity of the chamber, and in the case of a transmural infarction, preventing disastrous mechanical complications, such as cardiac rupture. In some cardiac diseases, cardiac fibrosis predominantly involves the interstitium and develops in the absence of significant cardiomyocyte loss. This process can occur in response to various insults, such as chronic inflammation, ischemia, or mechanical stress [9,10].

As mentioned before, cardiac hypertrophy is a phenomenon where the myocardium, the heart muscle increases in size. Hypertrophy of the cardiac muscle is an adaptive response to hemodynamic stress, which is believed to have a compensatory role in enhancing cardiac performance and diminishing ventricular wall tension and oxygen consumption. It can occur from various triggers, which are first and foremost classified as being either physiological or pathological. In essence, cardiac hypertrophy is classified as physiological when it is associated with normal cardiac function or as pathological when associated with cardiac dysfunction. Pathological hypertrophy is associated with fibrosis, capillary rarefaction, increased production of pro-inflammatory cytokines, dysfunction of normal signaling, suppression of autophagy, as well as unfavorable epigenetic changes. Pathological hypertrophy is characterized by reduced systolic and diastolic function, eventually leading to maladaptive cardiac remodeling and heart failure [10,11].

6.4.3. Microvascular changes

The vascular endothelium is composed of endothelial cells that function as a semipermeable barrier by forming the inner cellular lining of blood vessels. The endothelium is essential for maintaining vascular health and hemostasis, as it serves to inhibit clot formation and restore vascular homeostasis. It synthesizes nitric oxide, which protects against atherosclerosis, causes vasodilation by acting on vascular smooth muscles, regulates the formation of thrombi, and plays a role in fibrinolysis. When these processes are disturbed, the vasculature undergoes endothelial dysfunction. Endothelial dysfunction can be triggered directly through the signaling effects of the virus or indirectly by malfunction of the immunological response, leading to an inappropriate endothelial activation. This particular state of endothelial dysfunction caused by viral infections predisposes to coagulopathies and it is characterized by vascular leakage. The excess of free radicals disrupts the endothelial semipermeable barrier, reducing nitric oxide release, which in turn promotes vasoconstriction and allows penetration of toxins into the underlying tissues. The immune response hyperactivation due to SARS-CoV-2 infection causes an increased secretion of cytokines, endothelial dysfunction, and arterial stiffness, which promotes the development of atherosclerosis. In addition, COVID-19 induces a proinflammatory state, called a "cytokine storm". This is characterized by an excessive release of cytokines that have been observed in severe forms of the disease, further promoting vascular inflammation, endothelial dysfunction, disorders of coagulation, and cardiovascular complications. However, it is still under debate whether the inflammatory-associated changes are a direct effect of COVID-19 or a consequence of the "cytokine storm" [12].

VII. Mechanisms Underlying Myocardial Structural Changes

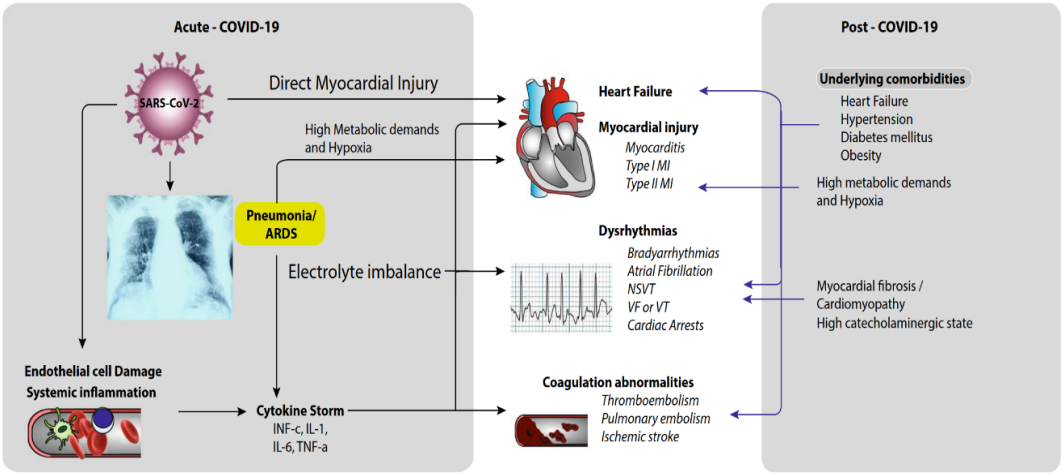

Figure 4. Summary of the Proposed Mechanisms for Myocardial Cell Injury by SARS-CoV-2 Infection. Direct injury might be caused by cell entry via the angiotensin-converting enzyme 2 (ACE2) protein expressed naturally on cardiomyocytes or endothelial cell damage (endotheliitis) due to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection. Indirect damage might be brought on by the hypercoagulability state of coronavirus disease-2019 (COVID-19), which engenders microthrombus formation, disrupting cardiac capillary flow or by means of T lymphocyte–mediated cytotoxicity as part of the phenomenon called cytokine storm.

7.1. Immunology of Covid 19 related to the cardiovascular system

Both direct viral infection and indirect injury resulting from inflammation, endothelial activation, and microvascular thrombosis occur in the context of COVID-19. What determines the extent of cardiovascular involvement is the amount of viral inoculum, the response from the host immune system, and the presence of underlying co-morbidities [13]. The suggested mechanisms of myocardial injury in patients with COVID-19 include myocardial damage by a cytokine storm triggered by an imbalanced response of T helper 1 cells (TH1 cells) and T helper 2 cells (TH2 cells) and respiratory dysfunction and hypoxemia caused by SARS-CoV-2 infection. Myocardial injury might also be attributable to decreased activity of the ACE2–Angiotensin 1–7 axis. ACE2 serves as the regulator of the renin-angiotensin system by metabolizing Angiotensin II, which is a vasoconstrictor and pro-inflammatory peptide, to the vasodilating angiotensin 1-7. Angiotensin 1-7 is a vasodilatory peptide with a cardiovascular protective function, as it serves as a counter-regulatory element of angiotensin II signaling [14].

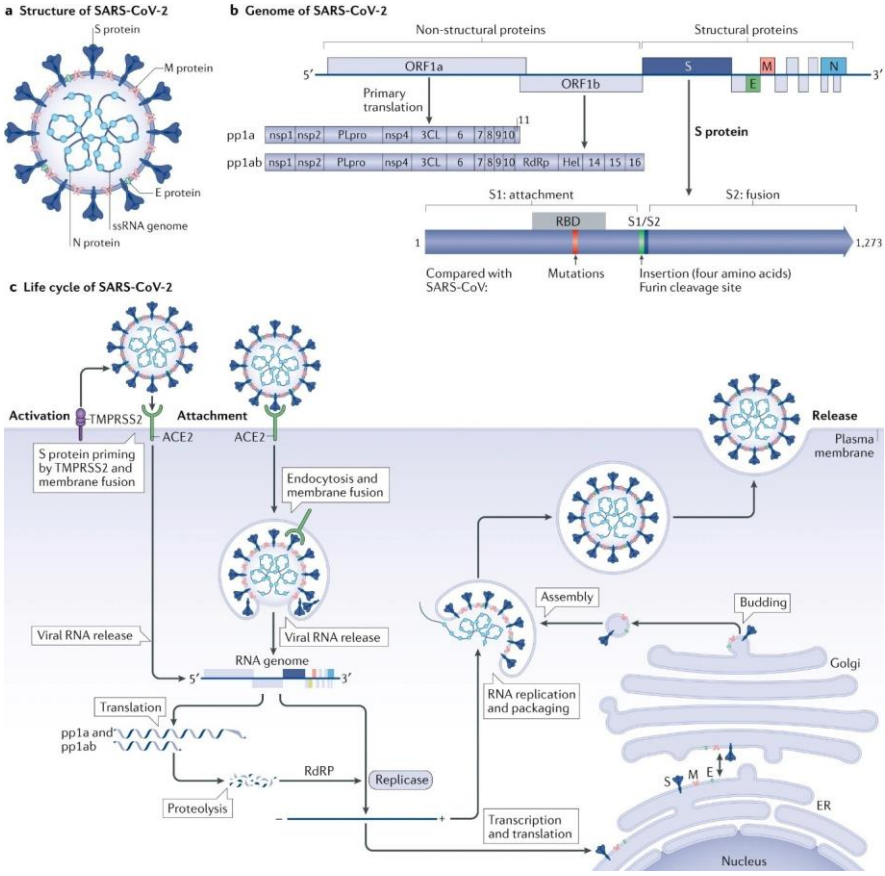

Figure 5. Structure, genome and life cycle of SARS-CoV-2. Coronaviruses form an enveloped spherical particle that consists of four structural proteins (spike (S), envelope (E), membrane (M) and nucleocapsid (N)) and a positive-sense, single-stranded RNA (ssRNA) genome that is 30 kb in length.The S protein consists of two subunits; the S1 subunit contains a receptor-binding domain that attaches and binds to angiotensin-converting enzyme 2 (ACE2) on the surface of host cells, whereas the S2 subunit function to facilitate the fusion between the membrane of the virus and the host cell. Infection by the SARS-CoV-2 is triggered by S protein binding to the ACE2 on the surface of host cells, and the viral complex is innternalized into the cytoplasm, undergoes translation and replication cycles. Lastly, the genomic RNA and sturctural proteins undergo assembly into new viral particles and are released via exocytosis.

7.1.1 Viral invasion of myocardial cells

ACE2 has been confirmed as the SARS-CoV-2 internalization receptor causing COVID-19, together with the host's transmembrane protease serine 2 (TMPRSS2), a membrane protease that primes the spike S protein of the virus to facilitate its cell entry. Once inside the cell, the virus uses the machinery of the host to translate RNA into polypeptides, including an RNA-dependent RNA polymerase that the virus uses to replicate its RNA. After the synthesis of structural proteins and assembly of particles, the new virus is released from the cell by exocytosis. Host cells may be disabled or destroyed in the process, potentially triggering an innate immune response [15]. There is also evidence in preclinical models using the SARS-CoV-2 virus of significant downregulation of ACE2 in the heart as a result of virus engagement in the ACE2 receptor during infection. This is likely part of the host defense mechanism in response to the infection to limit the continued proliferation of the virus. However, the potential consequence of this interaction is that the biologically essential role of ACE2 is also significantly diminished. This can lead to unopposed angiotensin II effects, including proinflammatory, prothrombotic, and pro-oxidant risks [16].

7.1.2. Inflammatory response

The SARS-CoV-2 infection can generate a diverse range of responses in patients, ranging from completely asymptomatic shedding of the virus to a severe inflammatory response, including a cytokine storm associated with high mortality. Analysis of the inflammatory response to SARS-CoV-2 is relatively limited. A consistent finding is lymphopenia occurring in up to 80% of patients. The degree of lymphopenia is a very important prognostic indicator early on in the course of infection. Among the most prominent findings in early analyses of patients succumbing to COVID-19 are reductions in circulating levels of CD4+ and CD8+ T lymphocytes. More specifically, a reduction in CD4+ more than CD8+ T cells. Recovery of lymphocyte count has been shown to coincide with clinical improvement. The important role of CD4+ T cells has been further delineated in a primary infection model with SARS-CoV in senescent mice. CD4+ T cells were found to enable the production of neutralizing antibodies and a balanced immune response. Without CD4+ T cells, there was much more severe interstitial pneumonitis [17,18,19].

Accompanying the loss of CD4+ T cells, there is an unusual macrophage predominance in SARS lung infiltration. Macrophages are a key component of the innate immune system, and they are a major source of the inflammatory cytokine tumor necrosis factor (TNF)-α. Activation of macrophages is driven by a disintegrin and metalloproteinase domain 17 (ADAM-17), a transmembrane protease, which is also responsible for the proteolysis and shedding of ACE2. In the setting of SARS-CoV-2 infection, membrane-bound ACE2 is internalized, leading to a decrease in receptor density. Because ACE2 is primarily responsible for the conversion of Angiotensin 2 to angiotensin 1-7, the loss of ACE2 receptor density and down-regulation of ACE2 leads to an accumulation of Angiotensin II. In turn, increased binding of Angiotensin 2 to the Angiotensin 2 type 1 receptor triggers a signalling cascade that leads to ADAM-17 phosphorylation and enhanced catalytic activity. Activated ADAM-17 increases ACE2 shedding, resulting in further reductions of Angiotensin II clearance, increased Angiotensin II-mediated inflammatory responses, and a veracious positive feedback cycle [13],[20]. This can be accompanied by hemophagocytosis in the lung and spleen, compatible with severe immune cytokine dysregulation. This syndrome results from the ineffective activation of cytotoxic CD8+ T lymphocytes and Natural Killer T lymphocytes, leading to an ineffective viral clearance and decreased antibody production. In turn, this stimulates further macrophage activation and the loop of self-amplification can be uncontrolled, leading to cytokine-storm syndrome and multiorgan failure. In patients with COVID-19 infection, in addition to lymphopenia, there appears to be a heightened level of interleukin 1 β (IL-1β) inflammatory response, in particular, in those with a poor prognosis. As the infection progresses, following IL-1β elevation, there is also increasing production of interleukin-6 (IL-6), which can precede an impending cytokine storm. In summary, there are potential early warning signs that indicate an impending dysfunctional immune response, such as lymphopenia, the release of troponin, elevated brain natriuretic peptides, and increasing inflammatory markers such as c-reactive protein, IL-1β, and IL-6 [20].

7.1.3. Microvascular dysfunction

ACE2 is expressed extensively throughout the circulatory system. Vascular smooth muscle co-expresses the ACE2 receptor and TMPRSS2. Similarly, arterial and venous endothelial cells are characterized by high levels of ACE2 receptors [21]. Viral replication in localized tissues elicits innate immune responses, resulting in macrophage activation of the M1 phenotype. Activated macrophages can release cytokines as mentioned above, including IL-1β and IL-6, which will promote the expression of adhesion molecules for endothelial activation, inflammatory infiltrates, and vascular inflammation. This can be locally enhanced if there is a smooth muscle cell harboring viral proliferation and cellular damage [22]. The release of interleukin (IL)-1β and IL-6 also promotes endothelial activation with the expression of cell adhesion molecules. Varga Z, et al reported that there`s histological evidence of "endotheliitis" caused by SARS-CoV-2 infection [23]. Inflamed and dysfunctional endothelium soon becomes adhesive and prothrombotic with increased expression of tissue factor and plasminogen activator inhibitor-1 [24]. In addition, significant elevations in von Willebrand factor levels have been observed in patients with severe COVID-19 infection, which suggests continuing endothelial activation and damage [25]. In addition, the presence of vasculitis and a prothrombotic state leads to an increased frequency of pulmonary embolism, which worsens hypoxemia by increasing shunting in these already highly hypoxemic patients with acute respiratory distress syndrome. This, in combination with systemic inflammatory or cytokine storm, can worsen cardiac injury, heart failure, and the prognosis.

VIII. Evidence of Myocardial Structural Changes in COVID-19

8.1. Histopathological findings

Histopathological findings in the context of cardiovascular manifestations of Covid 19 have been variable. One of the key questions is, whether these histopathological findings can be attributed to COVID-19, or are they caused by previous comorbidities, and to what extent their exacerbation could be attributed to COVID-19. In a systematic review by Hammoud H, et al., in the 23 articles that described heart pathology, the most commonly reported pathology was myocardial hypertrophy in 87 cases (51.2%), followed by myocardial fibrosis in 85 cases (50%), coronary small vessel disease in 44 cases (25.9%), myocardial cell infiltrate in 27 cases (15.9%), cardiac amyloidosis in 10 cases (5.9%), and myocardial necrosis in nine cases (5.3%) [26]. The causal relationship between COVID-19 and the aforementioned changes is impossible to establish, since no control studies before the COVID-19 infection were available.

COVID-19-associated myocarditis has been a topic of interest since the beginning of the pandemic. Initially, it was thought to be a relatively common cardiovascular complication of COVID-19 infection. Recent studies have however shed more light on its true prevalence, which may not be as high as first thought. Halushka, M et al. analyzed altogether 22 published studies with 277 post-mortem examinations to determine the prevalence of myocarditis in Covid 19. Classic myocarditis was identified in 7.2%, nonmyocarditis inflammatory infiltrate in 12.6%, single-cell ischemia in 13.7%, and acute myocardial infarction in 4.7%. At least one cardiovascular histopathologic abnormality such as a macrovascular or microvascular thrombus, inflammation, or intraluminal megakaryocytes was noted in 47.8%. After the initial studies in 2020 which reported COVID-19 myocarditis to occur in almost half of the cases, Halushka, M et al. reported that only 7.2% of the patients who died from COVID-19 had histological evidence of myocarditis. More importantly, most of these samples showed only small foci of inflammatory infiltrates of unknown clinical relevance in the myocardium. Multifocal or diffuse infiltrates with cardiomyocyte injury that would be expected to cause significant cardiac dysfunction were found in only 1.4% of the autopsied hearts [27]. Similarly, Almamlouk R,. et al. went through 19 studies with 217 cases and found that 36 cases had myocarditis according to the Dallas criteria, while 16 cases had inflammatory infiltrates but no myocyte damage [28]. Collectively, these data suggest that although fulminant myocarditis as a cause of death is rare (using histopathologic criteria), on the other hand, nonspecific cardiac inflammation and/or injury seems not to be. In addition, macrophage infiltrates have been reported in multiple studies in post-mortem autopsies. It is important to note that in most cases these infiltrates were not associated with cardiomyocyte injury, therefore they are classified as inflammatory infiltrates, and not true myocarditis, as defined by the Dallas criteria.

Microvascular dysfunction, vascular injury, and microthrombi have been a topic of interest as a possible mechanism of cardiovascular injury. In a systematic review by Menezes R., et al. evaluation of the blood vessels showed intimal and medial thickening together with luminal narrowing attributed to hypertrophic cardiomyopathy. Accumulation of inflammatory cells associated with the endothelium, as well as apoptotic bodies in the heart were also seen. Furthermore, there was some evidence of lymphocytic endotheliitis (inflammation of the blood vessels) and thrombosis of cardiac veins [29]. Pellegrini D et al. looked at microthrombi as the cause of cardiac injury and performed a study, where they conducted 40 pathological analyses on cardiac muscles. They report that 35% of subjects dying with COVID-19 had evidence of cardiac injury as identified by the presence of myocyte necrosis, with the majority (78.6%) having only focal myocyte necrosis. The major cause of myocyte necrosis was determined to be cardiac microthrombi, occurring in 64.3% of those with myocyte necrosis. Interestingly, they reported the microthrombi to be different in thrombus constituents, with increased fibrin and complement compared to intramyocardial thrombi from COVID-19–negative subjects and from thrombi aspirated from coronary arteries of both COVID-19–positive and –negative STEMI cases. They suggested that microvascular thrombosis should be entertained as a likely cause of cardiac injury in hospitalized patients with COVID-19 [30].

8.2. Imaging findings

Cardiovascular imaging, especially echocardiography and cardiac magnetic resonance imaging (CMR) has played an important part in characterizing and determining the cardiovascular complications of COVID-19. Multiple echocardiography measures, including left ventricular (LV) strain and right ventricular (RV) size and function, have been recognized as prognostic measures in patients with myocardial injury. Characterization of myocardial tissue on CMR is used to distinguish between ischemic and nonischemic types of myocardial injury in acute disease, as well as to identify subclinical disease in patients recovering from illness, including those affected by long-COVID syndrome (defined by the World Health Organization as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation). Imaging also provides a window into important pathophysiologic connections between acute and secondary diseases arising from COVID-19, including persisting myocardial abnormalities, endothelial and coronary microvascular dysfunction, and multiorgan abnormalities relevant to cardiovascular health. One of the first imaging studies was done by Szekely et al., who performed echocardiography in 100 hospitalized patients with COVID-19 in the spring of 2020. They reported RV dysfunction in 40% of patients, LV dysfunction in 10%, and diastolic dysfunction in 16%. In addition, subclinical LV dysfunction can be assessed on TTE by measuring global longitudinal strain (GLS) [31]. A meta-analysis of 38 studies reporting echocardiographic data in acute COVID-19 found that abnormal GLS was more frequent than overt LV dysfunction, with GLS appearing in 34% of cases compared to LV dysfunction in 25% [31].

As mentioned above, CMR has been used to characterize cardiac injury in COVID-19. Furthermore, since endomyocardial biopsy may not always be available or reasonable to diagnose myocarditis, CMR has been used more often. Cardiac MRI–based diagnosis of myocarditis has historically been based on the Lake Louise Criteria (LLC), which targets three aspects of myocardial inflammation: edema, hyperemia, necrosis, and/or fibrosis. A consistent reported finding in acute- and post-COVID-19 has been myocardial edema on CMR on T1 and/or T2 mapping or late-gadolinium enhancement (LGE), which enables the differentiation of viable from non-viable myocardium. In a study of 100 patients, 33% of whom were hospitalized due to COVID-19 and imaged a median of 71 days after testing positive for COVID-19, nonischemic LGE was found in 20%, prolonged native T1 relaxation time in 73%, and prolonged T2 relaxation time in 60%, respectively [32]. Croisier R,. et al. compared CMR findings of 25 young adults with acute COVID-19 and 1 or more markers of cardiac involvement (an abnormal electrocardiogram, elevated troponin, or cardiac symptoms), and used 25 healthy age- and sex-matched individuals as a control group. Furthermore, they divided the Covid-infected group into troponin-positive, and -negative groups. Median global longitudinal strain (GLS) and left ventricular ejection fraction (LVEF) were abnormal or reduced in the COVID-19 groups compared with control. Importantly, there was evidence for myocardial edema on T1 and T2 mapping in both troponin-positive and --negative cases compared with control subjects. Only 1 patient with COVID-19 had evidence of myocardial necrosis on LGE imaging. They suggested that COVID-19 illness is often characterized by

mild myocardial edema and inflammation without necrosis of the myocardium [33]. Effects of COVID-19 on the myocardium after recovery from initial infection have been a topic of interest, as subjective reports of cardiac issues from patients have been common. Huang L,. et al. presented a CMR study of 26 patients who had recovered from COVID-19 but reported cardiac symptoms. None of the 26 patients selected for this retrospective analysis had a known history of myocarditis or other heart pathologies before COVID-19. However, 15 of 26 patients showed myocardial edema and/or foci LGE lesion. The majority of T2 signal hyperintensity was found in the interventricular septum, anterior, anterior-lateral, and inferior walls. Furthermore, they suggested the location of edema caused by SARS-CoV-2 to appear different from those caused by other acute viral myocarditis, which commonly involves the inferior and inferior-lateral walls. Decreased right ventricle functional parameters including ejection fraction, cardiac index, and stroke volume/body surface area were found in patients with positive CMR findings [34].

IX. Long-Term Consequences of COVID-19 for cardiovascular health

As the COVID-19 pandemic was very recent, long-term consequences of the disease are still under examination and not many studies on the subject have been published. Xie Y et. al. looked at the long-term cardiovascular outcomes of Covid 19. This study involved 153,760 people with COVID-19, 5,637,647 contemporary controls, and 5,859,411 historical controls, which, altogether, correspond to 12,095,836 person-years of follow-up. They provided evidence that, beyond the first 30 days of infection, people with COVID-19 had increased risks and 12-month burdens of incident cardiovascular diseases, including cerebrovascular disorders, dysrhythmias, inflammatory heart disease, ischemic heart disease, heart failure, thromboembolic disease, and other cardiac disorders. These risks were evident regardless of age, race, sex, and other cardiovascular risk factors, including obesity, hypertension, diabetes, chronic kidney disease, and hyperlipidemia. Importantly, they were also present in people without any cardiovascular disease before exposure to COVID-19. This provides evidence that these risks might manifest even in people at low risk of cardiovascular disease [35]. Similarly, a retrospective cohort study with 4,131,717 participants divided into equal Covid-19-positive and -negative cases revealed that COVID-19 survivors faced significantly increased risks of developing various cardiovascular conditions, including cerebrovascular diseases, arrhythmia-related disorders, inflammatory heart diseases, ischemic heart diseases, other cardiac disorders, and thromboembolic disorders. In addition, the study also reported higher risks of major adverse cardiovascular events and any cardiovascular outcome in COVID-19 survivors compared to the control group, with a higher risk of mortality observed in elderly COVID-19 survivors (age $\geq$ 65 years) [36].

In the setting of COVID-19, myocarditis and cardiac myocyte damage can lead to residual morphologic and functional effects on the myocardium, particularly in those with pre-existing cardiovascular comorbidities. In a study from Germany, patients recently recovered from COVID-19 underwent CMR at a median of 71 days after COVID-19 infection. Lower left ventricular ejection fraction, higher left ventricular volumes, and higher native T1 (suggestive of myocardial interstitial fibrosis) and T2 (suggestive of myocardial edema) values were present in comparison with healthy control subjects and risk factor–matched control subjects [37]. In a multicenter study involving 148 COVID-19 survivors with elevated troponin who

underwent CMR after a median of 68 days following hospital discharge, the study reported a myocarditis-like LGE pattern in 26%, evidence of occlusive coronary disease in 22%, and dual pathology in 6%. Myocardial injury was limited to ≤3 of the 17 American Heart Association segments, and there was no measurable impact on left ventricular ejection fraction. Neither peak nor admission serum troponin was found to be predictive of a diagnosis of myocarditis [38]. Electrocardiographic and cardiac conduction abnormalities are not uncommon either among recovered patients with COVID-19 who had moderate to severe disease during their acute infection. Liu et al. reported that among 486 Chinese patients with COVID-19 followed at 3,6, and 12 months post-discharge, arrhythmias were present in 12.4%, 7.6%, and 16.3%, respectively. However, it is unclear how many of these abnormal electrocardiographic findings predated these patients' COVID-19 illness and, more importantly, which of these resulted from COVID-19 [39].

X. Management

10.1. Treatment of COVID-19 infection

The two main processes driving the pathogenesis of COVID-19 include replication of the virus in the early phase of the illness and dysregulated immune/inflammatory response to SARS-CoV-2 that leads to systemic tissue damage in the later phase of the disease. The guidelines, therefore, advise antiviral medications to halt viral replication in the early phase of the illness and immunomodulators in the later phase. The administration of antiviral medications depends on the patient`s overall health status, risk factors, and economic considerations. The risk of the patient developing a serious infection and the risk of being hospitalized needs to be accurately stratified. The list of risk factors associated with more severe COVID-19 that have conclusive evidence for them is extensive but includes common comorbidities such as asthma, DM1 and 2, chronic obstructive pulmonary disease, cancer, chronic kidney disease, underlying cardiovascular diseases such as heart failure, coronary artery disease, and diseases causing immunodeficiency such as HIV. For all patients independent of their status, general management of infectious diseases should be undertaken. Adequate caloric intake, bed rest, hydration, and antipyretic medication apply to everybody. When encountering a COVID-19 infection, the first question the clinician should ask is whether or not this patient requires supplemental oxygen. If not, the patient could at this time be managed at home. If they do require supplemental oxygen, antiviral agents should be considered. Management of hospitalized adults who do not require supplemental oxygen should include a prophylactic dose of anticoagulants, as they are more prone to thrombotic events due to the infection as well as increased immobility due to bed rest. In hospitalized patients, low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is preferred over oral anticoagulants. Because these types of heparin have shorter half-lives, their effects can be reversed quickly. They can also be administered intravenously or subcutaneously, and they have fewer drug-drug interactions than oral anticoagulants. When heparin is used, LMWH is preferred over UFH. Prophylactic doses of an LMWH agent, such as enoxaparin 40mg once a day in patients weighing under 100kg and 40mg twice a day in patients weighing more than 100kg, are commonly used. Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a platelet count <50,000 cells/µL, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, a history of a bleeding disorder, or an inherited or active

acquired bleeding disorder. Weighing the risk between thrombosis and the anticoagulant-induced bleeding event is often hard to determine in a clinical situation and consultation with a hematologist is warranted. In addition, the use of systemic corticosteroids in patients who are not hypoxic is advised against.

At the beginning of the pandemic, various drugs with suspected antiviral properties were used, such as hydroxychloroquine, an antimalarial drug, and azithromycin, a macrolide antibiotic. Despite their promising qualities early on, their use has significantly decreased as the scientific data to support their efficacy in Covid 19 was insufficient. National Institute of Health guidelines recommend the use of antivirals in the following order: 1) Ritonavir-boosted nirmatrelvir, sold under the brand name Paxlovid. 2) Remdesivir, 3) Molnupiravir. Ritonavir-boosted nirmatrelvir is a combination of oral protease inhibitors. It has been shown to reduce hospitalization and death when given to high-risk, unvaccinated, non-hospitalized patients. It must be given within 5 days of symptoms onset. The recommended dose is nirmatrelvir 300 mg with ritonavir 100 mg orally twice daily for 5 days, Remdesivir is a nucleotide analog that inhibits the SARS-CoV-2 RNA polymerase. The recommended duration of therapy in this setting is 3 days. The recommended dose is 200 mg IV on day 1, followed by 100 mg IV for 2 more days. Molnupiravir is a mutagenic ribonucleoside antiviral agent. Fetal toxicity has been reported in animal studies with this agent. Due to the risk of genotoxicity with this agent, it is not recommended in pregnant patients. This agent should only be used if both therapies are unavailable or cannot be given. For patients who require conventional oxygen therapy, the recommended treatment is dexamethasone plus remdesivir. Dexamethasone dose is 6 mg IV or oral (PO) once daily for up to 10 days or until hospital discharge. If the patient is on minimal oxygen, remdesivir monotherapy (without dexamethasone) should be used. If the patient is already receiving dexamethasone but has rapidly increasing oxygen needs and/or signs of systemic inflammation, oral baricitinib or intravenous (IV) tocilizumab should be added to the treatment regimen as these agents have been shown to improve outcomes in rapidly decompensating patients. Baricitinib or tocilizumab are also used as the next escalation step in patients who require more intense oxygen support with noninvasive ventilation, or even invasive measures to ensure adequate ventilation [40].

10.2. Management of cardiac manifestations of COVID-19

Management of the common cardiovascular manifestations of COVID-19 is per standard guidelines as they would be treated without COVID-19. Management of patients with myocardial involvement in the setting of COVID-19 is primarily dictated by the clinical presentation and course. Recognizing that the long-term consequences of this condition are not known, it is still reasonable to manage these individuals expectantly, with instruction to share any worrisome symptoms or signs (eg, chest pain, shortness of breath, syncope, edema) should they occur. Acknowledging the potential for overlap between some forms of myocardial involvement and possible myocarditis, patients who have chest pain as their only symptom, preserved LV systolic function, and no ventricular arrhythmias can likely be managed in the ambulatory setting with close monitoring for worrisome symptoms or signs (eg, shortness of breath, syncope, edema). Consideration should be given to follow-up testing (eg, ECG,

echocardiogram, ambulatory rhythm monitor, CMR) 3-6 months after presentation, particularly in those with ongoing cardiac symptoms and/or findings suggestive of significant/worsening myocardial involvement.

As mentioned above, due to the high rate of associated arterial thromboembolism and VTE, prophylactic anticoagulation is essential in the management of hospitalized patients with COVID-19. In patients who are diagnosed with myocardial injury, if necessary, heart rate should be controlled, usually by low-dose oral beta blockers and blood pressure lowering using ACEi/ARB. ESC guidelines recommend that the treatment of acute HF in patients with SARS-CoV-2 infection should be equivalent to those without COVID-19, and attention should be given to early detection and treatment of complications, including the need for noninvasive or invasive ventilation, bleeding events, and cardiac arrhythmias. Guideline-directed medical therapy [including angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) or sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonists, and other guideline-directed medications) should be continued in chronic HF patients, irrespective of COVID-19. Despite initial theoretical concerns regarding increased levels of ACE2 and the risk of acute COVID-19 with the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, treatment with angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers (ACEi/ARB) should be continued by patients with CVD, including treatment for HF and hypertension management. None of these agents affect susceptibility to SARS-CoV-2 infection or increase the risk of severe or fatal illness. They are safe and should be continued in patients with stable cardiovascular disease. On the contrary, withdrawal from guideline-directed medical therapy was associated with higher mortality in the acute to post-acute phase. Therefore, discontinuation of ACE inhibitors or ARBs is not recommended [40,41].

Treatment of myocarditis in stable patients should be based on standard pathways unrelated to COVID-19. A low-dose beta-blocker along with a renin-angiotensin-aldosterone system inhibitor may be used empirically in patients with mildly reduced LV systolic function and stable hemodynamics. In fact, Treatment with intravenous metoprolol tartrate was observed to improve respiratory status in a small, randomized trial of patients with COVID-19 and acute respiratory distress syndrome requiring mechanical ventilation. Beta-blockade can, however, precipitate cardiogenic shock in patients with greater compromise of cardiac function [42].

Treatment of arrhythmias depends on the type and severity of the arrhythmia. It may involve medications such as beta-blockers, calcium channel blockers, or antiarrhythmic drugs. In some cases, cardioversion or implantable devices like pacemakers or defibrillators may be necessary. Management of acute coronary syndrome involves standard treatments for ACS, including antiplatelet medications (such as aspirin and clopidogrel), anticoagulants, beta-blockers, nitroglycerin, and in some cases, reperfusion therapy such as thrombolytics or percutaneous coronary intervention (PCI) [40,41].

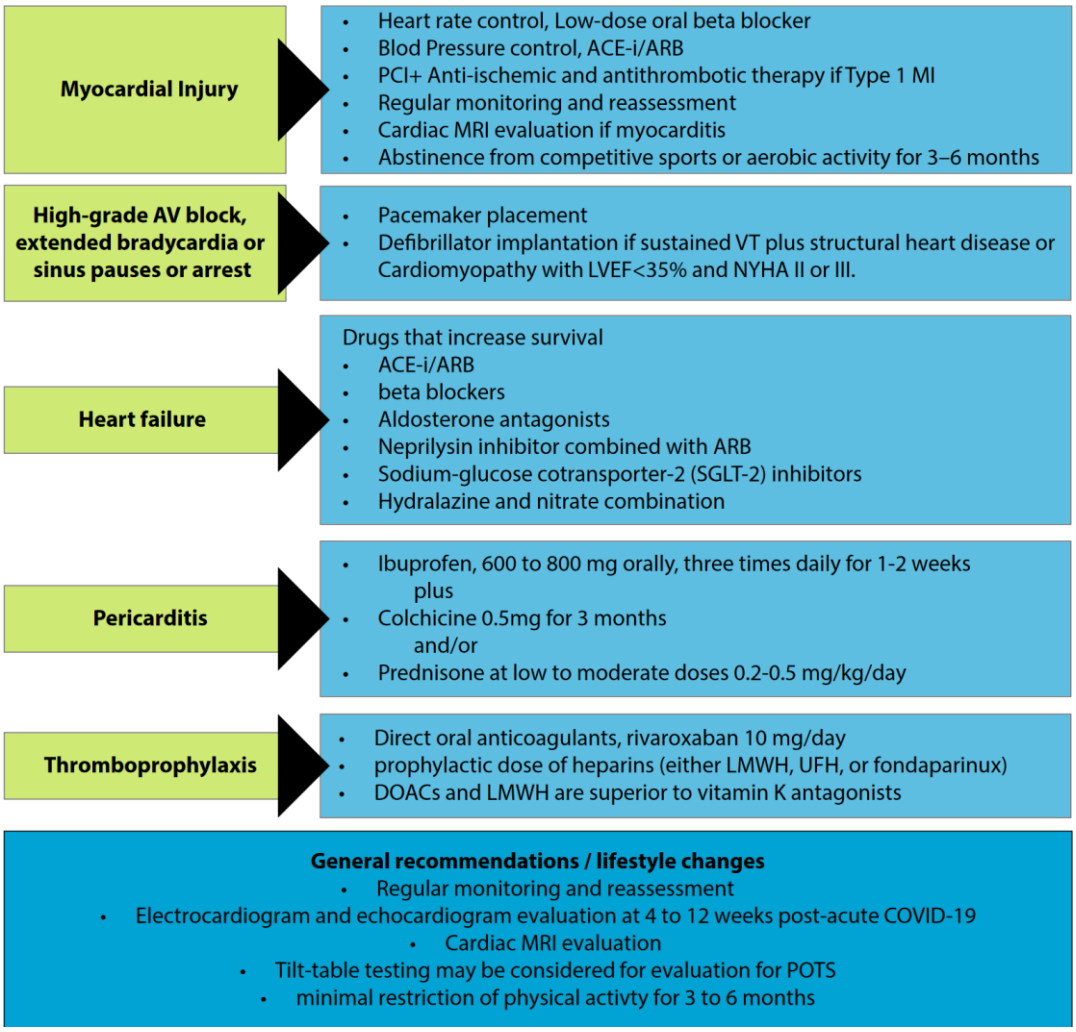

Figure 6. Post-acute COVID-19 management and general recommendations/lifestyle changes for cardiovascular manifestations of SARS-CoV-2 infection. PCI: percutaneous coronary intervention; ACE-i/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; MI: myocardial infarction; MRI: magnetic resonance imaging; VT: ventricular tachycardia; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association classification; LMWH: low-molecular-weight heparin; DOACs: direct oral anticoagulants; UFH: unfractionated heparin; POTS: postural orthostatic tachycardia syndrome

XI. Conclusion and Areas for future research

Cardiovascular complications in COVID-19 patients include acute myocardial injury, heart failure, pulmonary embolism, arrhythmias, acute coronary syndrome, and myocarditis. The structural changes in the myocardium associated with COVID-19 include myocardial edema, fibrosis, hypertrophy, as well as vascular injury. The driving factor of pathological manifestations seems to be an imbalanced immune system response to the virus and a cytokine storm disrupting physiological processes. Histopathological analysis of myocardial tissues has shown macrophage infiltration as well as inflammatory signs within the myocardium, but the prevalence of myocarditis per diagnostic criteria seems to be rare, while nonspecific inflammation is not. Microthrombi and coagulation abnormalities were noted early on during the pandemic, and there is conclusive evidence showing vascular inflammation and coagulation abnormalities in Covid-positive patients, which have significant cardiovascular implications such as pulmonary embolisms, strokes, and vein thromboses. Imaging modalities, mainly echocardiography and CMR have provided significant insight into the cardiovascular complications of Covid-19. LV strain has been recognized as an important prognostic feature for severe disease. Supporting the histopathological findings of inflammatory infiltrations, CMR of COVID-19-infected patients during and after the acute infection has shown edema of the myocardium on T1 and T2 mapping, as well as LGE. In large patient cohorts increased risks and 12-month burdens of incident cardiovascular diseases, including cerebrovascular disorders, dysrhythmias, inflammatory heart disease, ischemic heart disease, heart failure, thromboembolic disease, and other cardiac disorders. There has been evidence of these increased risks even in patients without known cardiovascular diseases, highlighting that the increased risk of future cardiovascular manifestations might concern low-risk individuals too.

As the pandemic occurred relatively recently, long-term studies on the risk of developing cardiovascular complications are fairly limited. Further studies on 12-month and longer follow-ups are needed to quantify the cardiovascular manifestations in patients after COVID-19. Furthermore, the causality of COVID-19 infection and its cardiovascular manifestations is still lacking. Evidence that patients with cardiovascular comorbidities are at an increased risk of suffering from severe COVID-19 infection and are at an increased risk of mortality, but further research is required to show causality between COVID-19 infection and the cardiovascular alterations and diseases as the majority of the studies conducted so far have not been able to identify underlying cardiovascular comorbidities. As the pandemic affected directly hundreds of millions of people, it gives an unprecedented amount of potential patient material for future investigations. Management of cardiovascular complications during COVID-19 infection is directed by guidelines independent of COVID-19, with sufficient evidence for them. More importantly, as the major pathophysiological trigger for organ dysfunction with COVID-19 seems to be an imbalanced immune system response, more focus should be put on the prognostic markers and novel treatments to decrease their incidence. The long-term impact of COVID-19 on cardiac health, including residual morphologic and functional myocardial impact remains a subject of ongoing research and clinical consideration.

XII. References

1. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, White JA, Abdel-Aty H, Gutberlet M, Prasad S, Aletras A, Laissy JP, Paterson I, Filipchuk NG, Kumar A, Pauschinger M, Liu P; International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol. 2009 Apr 28;53(17):1475-87. doi: 10.1016/j.jacc.2009.02.007. PMID: 19389557; PMCID: PMC2743893.

2. Tran DB, Weber C, Lopez RA. Anatomy, Thorax, Heart Muscles. 2022 Dec 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 31424779.

3. Ripa R, George T, Shumway KR, Sattar Y. Physiology, Cardiac Muscle. 2023 Jul 30. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 34283436.

4. Chaudhry R, Rahman S, Law MA. Anatomy, Thorax, Heart Arteries. 2023 Jul 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29261906.

5. Lampejo T, Durkin SM, Bhatt N, Guttmann O. Acute myocarditis: aetiology, diagnosis and management. Clin Med (Lond). 2021 Sep;21(5):e505-e510. doi: 10.7861/clinmed.2021-0121. PMID: 34507935; PMCID: PMC8439515.

6. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr, Olsen EG, Schoen FJ. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987 Jan;1(1):3-14. PMID: 3455232.

7. Rose NR. Learning from myocarditis: mimicry, chaos and black holes. F1000Prime Rep. 2014 May 6;6:25. doi: 10.12703/P6-25. PMID: 24904749; PMCID: PMC4018180.

8. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013 Sep;34(33):2636-48, 2648a-2648d. doi: 10.1093/eurheartj/eht210. Epub 2013 Jul 3. PMID: 23824828.

9. Frangogiannis NG. Cardiac fibrosis. Cardiovasc Res. 2021 May 25;117(6):1450-1488. doi: 10.1093/cvr/cvaa324. PMID: 33135058; PMCID: PMC8152700.

10. Hinderer S, Schenke-Layland K. Cardiac fibrosis - A short review of causes and therapeutic strategies. Adv Drug Deliv Rev. 2019 Jun;146:77-82. doi: 10.1016/j.addr.2019.05.011. Epub 2019 May 31. PMID: 31158407.

11. Shimizu I, Minamino T. Physiological and pathological cardiac hypertrophy. J Mol Cell Cardiol. 2016 Aug;97:245-62. doi: 10.1016/j.yjmcc.2016.06.001. Epub 2016 Jun 2. PMID: 27262674.

12. Ceasovschih A, Sorodoc V, Shor A, Haliga RE, Roth L, Lionte C, Onofrei Aursulesei V, Sirbu O, Culis N, Shapieva A, Tahir Khokhar MAR, Statescu C, Sascau RA, Coman AE, Stoica A, Grigorescu ED, Banach M, Thomopoulos C, Sorodoc L. Distinct Features of Vascular Diseases in COVID-19. J Inflamm Res. 2023 Jul 6;16:2783-2800. doi: 10.2147/JIR.S417691. PMID: 37435114; PMCID: PMC10332421.

13. Giustino G, Pinney SP, Lala A, Reddy VY, Johnston-Cox HA, Mechanick JI, Halperin JL, Fuster V. Coronavirus and Cardiovascular Disease, Myocardial Injury, and Arrhythmia: JACC Focus Seminar. J Am Coll Cardiol. 2020 Oct 27;76(17):2011-2023. doi: 10.1016/j.jacc.2020.08.059. PMID: 33092737; PMCID: PMC7572122.

14. Guo J, Huang Z, Lin L, Lv J. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Viewpoint on the Potential Influence of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on Onset and Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. J Am Heart Assoc. 2020 Apr 7;9(7):e016219. doi: 10.1161/JAHA.120.016219. Epub 2020 Apr 1. PMID: 32233755; PMCID: PMC7428639.

15. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020 Apr 16;181(2):281-292.e6. doi: 10.1016/j.cell.2020.02.058. Epub 2020 Mar 9. Erratum in: Cell. 2020 Dec 10;183(6):1735. PMID: 32155444; PMCID: PMC7102599.

16. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, Butany J. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009 Jul;39(7):618-25. doi: 10.1111/j.1365-2362.2009.02153.x. Epub 2009 May 6. PMID: 19453650; PMCID: PMC7163766.

17. Wang K, Gheblawi M, Oudit GY. Angiotensin Converting Enzyme 2: A Double-Edged Sword. Circulation. 2020 Aug 4;142(5):426-428. doi: 10.1161/CIRCULATIONAHA.120.047049. Epub 2020 Mar 26. PMID: 32213097.

18. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, Song S, Ma Z, Mo P, Zhang Y. Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia. J Infect Dis. 2020 May 11;221(11):1762-1769. doi: 10.1093/infdis/jiaa150. PMID: 32227123; PMCID: PMC7184346.

19. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020 May 1;130(5):2620-2629. doi: 10.1172/JCI137244. PMID: 32217835; PMCID: PMC7190990.

20. Liu PP, Blet A, Smyth D, Li H. The Science Underlying COVID-19: Implications for the Cardiovascular System. Circulation. 2020 Jul 7;142(1):68-78. doi: 10.1161/CIRCULATIONAHA.120.047549. Epub 2020 Apr 15. PMID: 32293910.

21. Hamming I, Cooper ME, Haagmans BL, Hooper NM, Korstanje R, Osterhaus AD, Timens W, Turner AJ, Navis G, van Goor H. The emerging role of ACE2 in physiology and disease. J Pathol. 2007 May;212(1):1-11. doi: 10.1002/path.2162. PMID: 17464936; PMCID: PMC7167724.

22. Boisramé-Helms J, Kremer H, Schini-Kerth V, Meziani F. Endothelial dysfunction in sepsis. Curr Vasc Pharmacol. 2013 Mar 1;11(2):150-60. PMID: 23506494.

23. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020 May 2;395(10234):1417-1418. doi: 10.1016/S0140-6736(20)30937-5. Epub 2020 Apr 21. PMID: 32325026; PMCID: PMC7172722.

24. Ekholm M, Kahan T. The Impact of the Renin-Angiotensin-Aldosterone System on Inflammation, Coagulation, and Atherothrombotic Complications, and to Aggravated COVID-19. Front Pharmacol. 2021 Jun 17;12:640185. doi: 10.3389/fphar.2021.640185. PMID: 34220496; PMCID: PMC8245685.

25. Escher R, Breakey N, Lämmle B. Severe COVID-19 infection associated with endothelial activation. Thromb Res. 2020 Jun;190:62. doi: 10.1016/j.thromres.2020.04.014. Epub 2020 Apr 15. PMID: 32305740; PMCID: PMC7156948.

26. Hammoud H, Bendari A, Bendari T, Bougmiza I. Histopathological Findings in COVID-19 Cases: A Systematic Review. Cureus. 2022 Jun 1;14(6):e25573. doi: 10.7759/cureus.25573. PMID: 35784976; PMCID: PMC9249248.

27. Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. Cardiovasc Pathol. 2021 Jan-Feb;50:107300. doi: 10.1016/j.carpath.2020.107300. Epub 2020 Oct 23. PMID: 33132119; PMCID: PMC7583586.

28. Almamlouk R, Kashour T, Obeidat S, Bois MC, Maleszewski JJ, Omrani OA, Tleyjeh R, Berbari E, Chakhachiro Z, Zein-Sabatto B, Gerberi D, Tleyjeh IM; Cardiac Autopsy in COVID-19 Study Group; Paniz Mondolfi AE, Finn AV, Duarte-Neto AN, Rapkiewicz AV, Frustaci A, Keresztesi AA, Hanley B, Märkl B, Lardi C, Bryce C, Lindner D, Aguiar D, Westermann D, Stroberg E, Duval EJ, Youd E, Bulfamante GP, Salmon I, Auer J, Maleszewski JJ, Hirschbühl K, Absil L, Barton LM, Ferraz da Silva LF, Moore L, Dolhnikoff M, Lammens M, Bois MC, Osborn M, Remmelink M, Nascimento Saldiva PH, Jorens PG, Craver R, Aparecida de Almeida Monteiro R, Scendoni R, Mukhopadhyay S, Suzuki T, Mauad T, Fracasso T, Grimes Z. COVID-19-Associated cardiac pathology at the postmortem evaluation: a collaborative systematic review. Clin Microbiol Infect. 2022 Aug;28(8):1066-1075. doi: 10.1016/j.cmi.2022.03.021. Epub 2022 Mar 23. PMID: 35339672; PMCID: PMC8941843.

29. Menezes RG, Rizwan T, Saad Ali S, Hassan W, Khetpal A, Aqil M, Madadin M, Jamal Siddiqi T, Shariq Usman M. Postmortem findings in COVID-19 fatalities: A systematic review of current evidence. Leg Med (Tokyo). 2022 Feb;54:102001. doi: 10.1016/j.legalmed.2021.102001. Epub 2021 Dec 7. PMID: 34952452; PMCID: PMC8648585.

30. Pellegrini D, Kawakami R, Guagliumi G, Sakamoto A, Kawai K, Gianatti A, Nasr A, Kutys R, Guo L, Cornelissen A, Faggi L, Mori M, Sato Y, Pescetelli I, Brivio M, Romero M, Virmani R, Finn AV. Microthrombi as a Major Cause of Cardiac Injury in COVID-19: A Pathologic Study. Circulation. 2021 Mar 9;143(10):1031-1042. doi: 10.1161/CIRCULATIONAHA.120.051828. Epub 2021 Jan 22. PMID: 33480806.

31. Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, Gal Oz A, Rothschild E, Baruch G, Peri Y, Arbel Y, Topilsky Y. Spectrum of Cardiac Manifestations in COVID-19: A Systematic Echocardiographic Study. Circulation. 2020 Jul 28;142(4):342-353. doi: 10.1161/CIRCULATIONAHA.120.047971. Epub 2020 May 29. PMID: 32469253; PMCID: PMC7382541.

32. Park J, Kim Y, Pereira J, Hennessey KC, Faridi KF, McNamara RL, Velazquez EJ, Hur DJ, Sugeng L, Agarwal V. Understanding the role of left and right ventricular strain assessment in patients hospitalized with COVID-19. Am Heart J Plus. 2021 Jun;6:100018. doi: 10.1016/j.ahjo.2021.100018. Epub 2021 Jun 1. PMID: 34095889; PMCID: PMC8168299.

33. Crosier R, Kafil TS, Paterson DI. Imaging for Cardiovascular Complications of COVID-19: Cardiac Manifestations in Context. Can J Cardiol. 2023 Jun;39(6):779-792. doi: 10.1016/j.cjca.2023.01.022. Epub 2023 Jan 31. PMID: 36731604; PMCID: PMC9886397.

34. Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC Cardiovasc Imaging. 2020 Nov;13(11):2330-2339. doi: 10.1016/j.jcmg.2020.05.004. Epub 2020 May 12. PMID: 32763118; PMCID: PMC7214335.

35. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022 Mar;28(3):583-590. doi: 10.1038/s41591-022-01689-3. Epub 2022 Feb 7. PMID: 35132265; PMCID: PMC8938267.

36. Wang W, Wang CY, Wang SI, Wei JC. Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: A retrospective cohort study from the TriNetX US collaborative networks. EClinicalMedicine. 2022 Nov;53:101619. doi: 10.1016/j.eclinm.2022.101619. Epub 2022 Aug 11. Erratum in: EClinicalMedicine. 2023 May;59:101968. PMID: 35971425; PMCID: PMC9366236.

37. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Nov 1;5(11):1265-1273. doi: 10.1001/jamacardio.2020.3557. Erratum in: JAMA Cardiol. 2020 Nov 1;5(11):1308. PMID: 32730619; PMCID: PMC7385689.

38. Raisi-Estabragh Z, McCracken C, Cooper J, Fung K, Paiva JM, Khanji MY, Rauseo E, Biasiolli L, Raman B, Piechnik SK, Neubauer S, Munroe PB, Harvey NC, Petersen SE. Adverse cardiovascular magnetic resonance phenotypes are associated with greater likelihood of incident coronavirus disease 2019: findings from the UK Biobank. Aging Clin Exp Res. 2021 Apr;33(4):1133-1144. doi: 10.1007/s40520-021-01808-z. Epub 2021 Mar 8. PMID: 33683678; PMCID: PMC7938275.

39. Liu T, Wu D, Yan W, Wang X, Zhang X, Ma K, Chen H, Zeng Z, Qin Y, Wang H, Xing M, Xu D, Li W, Ni M, Zhu L, Chen L, Chen G, Qi W, Wu T, Yu H, Huang J, Han M, Zhu W, Guo W, Luo X, Chen T, Ning Q. Twelve-Month Systemic Consequences of Coronavirus Disease 2019 (COVID-19) in Patients Discharged From Hospital: A Prospective Cohort Study in Wuhan, China. Clin Infect Dis. 2022 Jun 10;74(11):1953-1965. doi: 10.1093/cid/ciab703. PMID: 34390330; PMCID: PMC9187317.

40. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [19.4.2024]

41. Writing Committee; Gluckman TJ, Bhave NM, Allen LA, Chung EH, Spatz ES, Ammirati E, Baggish AL, Bozkurt B, Cornwell WK 3rd, Harmon KG, Kim JH, Lala A, Levine BD, Martinez MW, Onuma O, Phelan D, Puntmann VO, Rajpal S, Taub PR, Verma AK. 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022 May 3;79(17):1717-1756. doi: 10.1016/j.jacc.2022.02.003. Epub 2022 Mar 16. PMID: 35307156; PMCID: PMC8926109.

42. Clemente-Moragón A, Martínez-Milla J, Oliver E, Santos A, Flandes J, Fernández I, Rodríguez-González L, Serrano Del Castillo C, Ioan AM, López-Álvarez M, Gómez-Talavera S, Galán-Arriola C, Fuster V, Pérez-Calvo C, Ibáñez B. Metoprolol in Critically Ill Patients With COVID-19. J Am Coll Cardiol. 2021 Sep 7;78(10):1001-1011. doi: 10.1016/j.jacc.2021.07.003. PMID: 34474731; PMCID: PMC8404624.

References of Figures:

Figure 4. Summary of the Proposed Mechanisms for Myocardial Cell Injury by SARS-CoV-2 Infection. **Siripanthong B, Asatryan B, Hanff TC, Chatha SR, Khanji MY, Ricci F, Muser D, Ferrari VA, Nazarian S, Santangeli P, Deo R, Cooper LT Jr, Mohiddin SA, Chahal CAA**. The Pathogenesis and Long-Term Consequences of COVID-19 Cardiac Injury. JACC Basic Transl Sci. 2022 Mar;7(3):294-308. doi: 10.1016/j.jacbts.2021.10.011. Epub 2022 Feb 9. PMID: 35165665; PMCID: PMC8828362.

Figure 5. Structure, genome and life cycle of SARS-CoV-2. **Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC**. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020 Sep;17(9):543-558. doi: 10.1038/s41569-020-0413-9. Epub 2020 Jul 20. PMID: 32690910; PMCID: PMC7370876.

Figure 6. Post-acute COVID-19 management and general recommendations/lifestyle changes for cardiovascular manifestations of SARS-CoV-2 infection. **Kole C, Stefanou E, Karvelas N, Schizas D, Toutouzas KP**. Acute and Post-Acute COVID-19 Cardiovascular Complications: A Comprehensive Review. Cardiovasc Drugs Ther. 2023 May 20:1–16. doi: 10.1007/s10557-023-07465-w. Epub ahead of print. PMID: 37209261; PMCID: PMC10199303.