COVID-19 Vaccine–Related Myocardial and Pericardial Inflammation

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Abstract
Purpose of Review To review myocarditis and pericarditis developing after COVID-19 vaccinations and identify the management strategies.

Recent Findings COVID-19 mRNA vaccines are safe and effective. Systemic side effects of the vaccines are usually mild and transient. The incidence of acute myocarditis/pericarditis following COVID-19 vaccination is extremely low and ranges 2–20 per 100,000. The absolute number of myocarditis events is 1–10 per million after COVID-19 vaccination as compared to 40 per million after a COVID-19 infection. Higher rates are reported for pericarditis and myocarditis in COVID-19 infection as compared to COVID-19 vaccines.

Summary COVID-19 vaccine–related inflammatory heart conditions are transient and self-limiting in most cases. Patients present with chest pain, shortness of breath, and fever. Most patients have elevated cardiac enzymes and diffuse ST-segment elevation on electrocardiogram. Presence of myocardial edema on T2 mapping and evidence of late gadolinium enhancement on cardiac magnetic resonance imaging are also helpful additional findings. Patients were treated with non-steroidal anti-inflammatory drugs and colchicine with corticosteroids reserved for refractory cases. At least 3–6 months of exercise abstinence is recommended in athletes diagnosed with vaccine-related myocarditis. COVID-19 vaccination is recommended in all age groups for the overall benefits of preventing hospitalizations and severe COVID-19 infection sequela.

Keywords COVID-19 vaccination · Pericarditis · Myocarditis · SARS-CoV-2 · Myopericarditis

Introduction
The incidence of myocarditis and pericarditis in the general population ranges from 2 to 20 individuals per 100,000 per year and is more common among males [1–3]. A higher incidence of myocarditis, up to 36.5 per 100,000, is also reported in some population-based studies [4]. The most common etiology of these two conditions in the developed world is viral or idiopathic, and adenoviruses, enteroviruses, parvovirus B19, herpesviridae, Influenza, HIV, hepatitis C, and HIV are commonly identified viruses [1]. Coronavirus are also found to be associated with inflammatory diseases of the heart. Recently, SARS-CoV-2 was identified to cause myocarditis and pericarditis. Additionally, cases of COVID19 vaccine-associated myocarditis (COVID19VAM) and COVID19 vaccine-related pericarditis (COVID19VAP) are also reported. Interestingly, inflammatory heart conditions have also been previously reported as an adverse reaction to influenza and hepatitis B vaccinations [5]. This review focuses on the inflammatory heart diseases related to COVID19 vaccinations with a brief summary of available cases.

COVID-19 Vaccine–Related Inflammatory Heart Diseases
COVID-19 mRNA vaccines are safe and effective as several large-scale clinical trials confirmed that these vaccines improve patient outcomes and disease severity [6, 7]. Systemic side effects of the vaccines are usually mild, transient,
and more commonly reported in younger populations [8]. Although autoimmune reactions and inflammatory heart diseases are rare, there is growing literature describing these infrequent side effects arising from COVID-19 vaccines, particularly mRNA vaccines.

The adverse events regarding vaccinations in the USA are documented in the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system for early reporting of potential adverse effects [9]. Oster et al. analyzed VAERS with the data of approximately 350 million mRNA-based COVID-19 vaccine administrations. They identified 1991 cases, of which 1626 met the case definition for myocarditis of which only 391 had pericarditis. Pericarditis without myocardial involvement was reported in 684 patients. The rates were highest after the second dose of the COVID-19 vaccine and predominantly young males between the age of 12 and 24 years were affected. The reporting rates were lower in females than males across all age strata aged younger than 50 years [10]. The percentage of males and the age group of the recipients presenting with myopericarditis were similar to pre-COVID 2019 era documentation in the VAERS associated with other vaccinations. However, VAERS is susceptible to reporting bias, affected by various factors such as general awareness of the adverse effects [11]. CDC also reported myocarditis associated with COVID 2019 mRNA vaccines from Pfizer-BioNTech and Moderna. The data from CDC showed an increased risk of myopericarditis among recipients between 12 and 39 years of age within 7 days of receiving the COVID-19 vaccine compared to unvaccinated individuals or those who received non-mRNA COVID-19 vaccines on the same days. The findings were consistent with the CDC dataset and several other epidemiological studies [12–15]. Witberg et al. found the rate of vaccine-related myocarditis almost five times more prevalent in 16–29-year-old population (10.69 per 100,000) compared to the general population (2.13 per 100,000) [12]. However, the rate of COVID-19 vaccine myopericarditis in the male population between 12 and 39 years was reported to be 1.8 per 100,000 by Husby et al. and up to 19% in adolescents aged between 12 and 17 years by Chua et al. [13, 15]. A study conducted in the UK included around 10 million vaccinated individuals and showed that myocarditis was more common in males less than 40 years of age who received two doses of the Moderna vaccine (113 cases per million) compared to 3 doses of the Pfizer vaccine (28 cases per million) [14].

**Proposed Pathophysiologic Mechanisms of COVID-19 Vaccine–Related Pericardial and Myocardial Inflammation**

The Pfizer-BioNTech and Moderna vaccines use modified mRNA packaged in a lipid nanoparticle and injected intramuscularly into the human body. Upon attaching to the host cell, the nanoparticle inserts mRNA into the cytoplasm that travels to the ribosomes to synthesize viral spike proteins (translation) [16]. These newly synthesized proteins are degraded by proteasomes into antigenic peptides. These antigenic peptides are expressed on the cellular membrane through the major histocompatibility complex (MHC) class I to interact with CD8+ cytotoxic T cells. The translated proteins also gain entry into the antigen-presenting cells (APCs) and are expressed on the cellular surface by MHC class II. T-cell receptor (TCR) membrane protein and CD4 proteins of CD4+ T cells interact with the MHC class II to produce cytokines such as IL-2, IL-4, and IL5 and activate cellular immunity. This interaction also activates humoral immune response by triggering the differentiation of the B cells that in turn release a significant amount of antibodies against the viral spike proteins [17]. Additionally, innate immune response is also activated when RNA in mRNA vaccines binds to Toll-like receptor (TLR) and produces type-I interferon.

The AstraZeneca and Johnson & Johnson vaccines have a similar mechanism of action. These vaccines use a modified chimpanzee DNA adenovirus. This does not create an immune response to adenovirus but only to the viral protein encoded in the host DNA. The DNA vector encodes a protein similar to viral s-protein and migrates to cell nucleus and utilizes host enzymes to convert to mRNA. Host cell ribosomes interact with this mRNA resulting into translated proteins that are expressed on cell membranes by MHC. The mechanism of DNA vaccines are similar to RNA vaccines from this point. The interaction of T cells with MHC as described above leads to the activation of B cells, T cells, and plasma cells to form antibodies against the viral proteins [16].

Various mechanisms are proposed for vaccine-induced myocarditis and pericarditis, including hyper-activation of the immune system, molecular mimicry, and differences of sex hormones. Figure 1 describes the possible pathophysiological mechanisms including hyper-inflammation, molecular mimicry, and hormonal differences.
Hyper-inflammation

SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA that encodes the viral spike glycoprotein of the virus. The vaccine does not contain live viruses or DNA [18]. Nucleoside modifications of mRNA have been shown to reduce innate immunogenicity. Usually, the tendency of dendritic cells or Toll-like receptor (TLR) expressing cells to express and activate cytokines markers is markedly less when exposed to mRNA with nucleoside modifications versus when treated with unmodified RNA. However, in selected individuals with genetic tendencies, the immune response to mRNA may still accelerate the activation of both innate and acquired immune responses [19].

The dendritic cells or TLR expressing cells exposed to ribonucleic acid (RNA) can excessively express and activate cytokines markers in some individuals with genetic inclination. The immune system may therefore detect the mRNA in the vaccine as an antigen, resulting in hyper-activation of inflammatory cascades leading to the development of myocardial and pericardial inflammation [19].

Bystander Activation

Virus-specific CD8+ T cells migrate to the target tissue infected with the viral infection and activate perforin and granzyme-mediated cytotoxicity. Reactive oxygen species (ROS) and nitric oxide that are released by adjacent macrophages also incur damage to the surrounding tissues. Additionally, pro-inflammatory cytokines that are released by CD4+ cells also enhance the phagocytic function of macrophages [20]. This bystander activation, dysregulated lymphocyte proliferation, and ineffective clearance of killed cells expose autoantigens and contribute to the generation of autoreactive cells [21]. In severe COVID-19 cases, lymphocytes are accumulated at the site of viral infection and activate bystander killing of adjacent non-infected cells by releasing pro-inflammatory cytokines and ROS. Autopsy reports of COVID-19 patients showed lymphocytic infiltration in the lungs, heart, kidney, and liver suggesting bystander activation [22]. Similar mechanism may be implicated in COVID-19 vaccines. It has been shown that CD8+ T cells response is mostly apparent...
only after the second dose of vaccination in addition to the increased quantity of CD4 + cells in infection-naïve individuals [23]. This corresponds to a higher number of inflammatory heart diseases primarily identified after the second dose in the epidemiological studies, but data exploring pathophysiological basis of these rare COVID-19 vaccine side effects is lacking.

**Molecular Mimicry**

Molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens is another potential mechanism that may result in myocarditis following vaccination [6]. Antibodies against spike glycoproteins have been shown to cross-react with similar human peptide proteins including α-myosin. The COVID-19 vaccine does not appear to commence de novo immune-mediated adverse events. Instead, certain individuals with genetic susceptibility may have dysregulated immune pathways at baseline which may be aggravated following vaccination against COVID-19. This may result in polyclonal B cell expansion, immune complex formation, and further inflammation [19].

**Autoantibodies and Anti-idiotype Antibodies**

According to the Network Hypothesis, antibody response against an antigen induces downstream antibody response against the antigen-specific antibody. In other words, initial antibody induced by the antigen (Ab1) has immunogenic regions called idiotopes that may trigger antibodies against Ab1 antibody. These antibodies, known as Ab2 antibodies, may structurally mimic Ab1 antibodies or the original viral antigen. Neutralization of Ab1 antibodies by forming immune complexes, up/downregulate the ACE2 receptors directly, and mimicking the viral particles are various mechanisms by which these autoantibodies may affect the affected or normal cells [24]. This type of anti-idiotype response is previously implicated in autoimmune arising after viral infection and preclinical studies of Ab2-induced autoimmune myocarditis [25]. However, the exact role of anti-idiotype antibody response is not investigated in the context of COVID-19 vaccines and needs further exploration.

**Sex Hormones**

Male prevalence in myopericarditis cases has been illustrated before, and the reasons remain unknown. Majority of the reported cases of COVID19 vaccine related inflammatory heart conditions were male (Table 1), and the underlying sex hormonal differences may be responsible for this gender distribution. Testosterone has been shown to play a role by commitment to a Th1-type immune response [26]. Estrogen’s inhibitory effects on pro-inflammatory T cells result in diminished cell-mediated immune responses, and the incidence of pericarditis is higher during the post-menopausal period in women [27]. Stimulating effect of testosterone and inhibitory effect of estrogen on the inflammatory cells in combination may explain an increased risk of developing myo-pericardial inflammation secondary to COVID19 vaccination.

**Clinical Manifestations and Diagnostic Findings**

The clinical manifestations and course of myocarditis and pericarditis are variable. Myocarditis may range from sub-clinical disease to fatigue, chest pain, heart failure, ventricular arrhythmias, cardiogenic shock, and rarely death [28–30]. Acute myocarditis is defined as the development of symptoms of heart failure (dyspnea, orthopnea, and lower extremity edema) over 3 months or less, while chronic myocarditis is when these symptoms persist over 3 months [31]. The clinical diagnosis of acute pericarditis requires two of the following criteria: (1) sharp, pleuritic positional chest pain; (2) pericardial friction rub; (3) new diffuse ST elevation or PR depression; and (4) pericardial effusion [32].

Table 1 summarizes 88 patients published in the literature as of April 2022. Out of these cases, 67 patients ≤ 18 years, and 81 (92%) were males. All the cases of vaccine-related pericarditis and myocarditis were after mRNA vaccination. Only 17 (19%) cases happened after receiving the first dose, and the rest occurred after the second dose of the vaccine. The most common symptoms included chest pain, shortness of breath, and fever. The onset of symptoms varied extensively among all cases, ranging from hours to as long as 39 days after vaccine administration. In the published cases, all but one patient did not have evidence of elevated cardiac enzymes. The most common electrocardiogram (ECG) finding was diffuse ST-segment elevation in 53 patients (60%), followed by diffuse non-specific ST-segment changes in five patients (6%), and other changes included T-wave inversions, ST-segment depression, junctional rhythm, and left bundle branch block (Table 2). A total of 17 patients (22%) had normal ECGs. Most patients underwent further evaluation with dedicated transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (CMR). TTE findings were normal in two-thirds of the patients. Among the rest of the cases, there was heterogeneity in the echocardiographic findings. Pericardial effusions were found in only...
six patients (7%). There were eight (9%) patients noted to have a reduced left ventricle (LV) function, of which seven were ≤ 18 years. CMR was available in 63 patients (72%), and the presence of myocardial edema on T2 mapping was seen in 55 patients. Evidence of late gadolinium enhancement (LGE) was only present in three patients. Additionally, five cases showed evidence of myocardial fibrosis. However, there were five (6%) patients who had no evidence of acute myocarditis and or pericarditis upon imaging (Table 2).

Management of Vaccine-Induced Pericarditis and Myocarditis

A higher degree of suspicion is warranted to clinically identify these patients as they may present without typical cardiac symptoms and signs of chest pain or dyspnea. The diagnosis of myocarditis should be suspected in patients with elevated cardiac biomarkers (e.g., troponin, BNP, or NT-proBNP) and new ST-segment changes suggestive of myocardial injury on the ECG or new onset impaired systolic left ventricle systolic function in the absence of underlying ischemic changes [55]. Pericardial effusion may be an initial clue on the point of care ultrasound examination and should raise suspicion for pericarditis in an appropriate clinical setting. Patients with pericardial and myocardial inflammation have overlapping features and may present as a spectrum of myopericarditis or perimyocarditis [56].

COVID-19 vaccine–related myopericarditis is transient and self-limiting in most cases. Upon review of the 88 patients, the onset of symptoms after exposure was shorter for COVID19VAM compared to a typical viral illness. These cases were typically diagnosed within a few days of receiving the vaccination, and in one particular case, the symptoms occurred within a few hours of vaccine administration. Majority of the cases were treated with non-steroidal anti-inflammatory drugs (NSAIDs) alone. Some patients did require dual therapy with either an NSAID with colchicine or an NSAID with glucocorticoids. In a minority

### Table 1  Studies reporting myocardial or pericardial inflammation in individuals receiving COVID-19 vaccine

| Study (Last name of first author followed by year published) | No. of patients | Age (avg) | Gender (x male, y female) | Symptoms | Vaccine | Dose | Days after vaccine (avg) |
|-------------------------------------------------------------|-----------------|-----------|---------------------------|----------|---------|------|------------------------|
| Ambati 2021 [33]                                              | 2               | 17        | 2 M                       | Chest pain, fatigue, fever | Pfizer-BioNTech | 2nd  | 2                     |
| Fleming-Nouri 2021 [34]                                       | 7               | 21        | 7 M                       | Chest pain               | Pfizer-BioNTech | 2nd  | 3                     |
| Sakaguchi 2021 [35]                                           | 1               | 49        | 1 M                       | Fever, cough, orthopnea  | Pfizer-BioNTech | 2nd  | 2                     |
| Chen 2021 [36]                                                | 1               | 16        | 1 M                       | fever, chest pain, myalgia | Pfizer-BioNTech | 1st   | 4                     |
| Das 2021 [37]                                                 | 25              | 15        | 24 M, 1 F                 | Chest pain, dysnea, fatigue, chills | Pfizer-BioNTech | 2nd  | 3                     |
| Nygaard 2022 [38]                                             | 15              | 17        | 13 M, 2 F                 | Chest pain               | Pfizer-BioNTech | 2nd  | 2                     |
| Bartlett 2021 [39]                                            | 1               | 46        | 1 M                       | Fever, chest pain        | Pfizer-BioNTech | 2nd  | 1                     |
| Badshah 2021 [40]                                             | 1               | 22        | 1 F                       | Chest pain, chills       | Moderna         | 2nd  | 1                     |
| Hung 2022 [41]                                                | 1               | 23        | 1 M                       | Fever, sore throat, myalgia | AstraZeneca/Oxford | 1st | 7                     |
| McLean 2021 [42]                                              | 1               | 16        | 1 M                       | Chest pain               | Pfizer-BioNTech | 2nd  | 3                     |
| Schauer 2021 [43]                                             | 13              | 15        | 13 M                      | Chest pain, fever, headache, myalgia | Pfizer-BioNTech | 2nd  | 3                     |
| Farooq 2022 [44]                                              | 1               | 63        | 1 M                       | Dyspnea, chest tightness | AstraZeneca/Oxford | 2nd  | 35                    |
| Umei 2021 [45]                                                | 1               | 20        | 1 M                       | Fever, myalgia           | Moderna         | 2nd  | 2                     |
| Kim 2021 [46]                                                 | 1               | 29        | 1 M                       | Fever, chest pain        | Pfizer-BioNTech | 2nd  | 4                     |
| Ameratunga 2022 [47]                                          | 1               | 57        | 1 F                       | Lethargy, dysnea         | Pfizer-BioNTech | 1st   | 3                     |
| Ashaari 2021 [48]                                             | 1               | 66        | 1 M                       | Chest pain, fatigue      | Pfizer-BioNTech | 1st   | 7                     |
| D’Angelo 2021 [49]                                            | 1               | 30        | 1 M                       | Chest pain, shortness of breath | Pfizer-BioNTech | 2nd  | 2                     |
| Marshall 2021 [50]                                            | 7               | 17        | 7 M                       | Chest pain               | Pfizer-BioNTech | 2nd  | 3                     |
| Facetti 2021 [51]                                             | 1               | 20        | 1 M                       | Chest pain               | Pfizer-BioNTech | 2nd  | 3                     |
| King 2021 [52]                                                | 4               | 25        | 4 M                       | Chest pain, pleuritic    | Moderna         | 2nd  | 4                     |
| Hasnie 2021 [53]                                              | 1               | 22        | 1 M                       | Chest pain               | Moderna         | 1st   | 3                     |
| Patrignani 2021 [54]                                          | 1               | 56        | 1 M                       | Abdominal and chest pain | Pfizer-BioNTech | 1st   | 4                     |
| Study (Last name of first author followed by year published) | EKG changes | Elevation of cardiac enzymes | Echocardiography findings | MRI findings | Management | Outcomes |
|-------------------------------------------------------------|-------------|------------------------------|---------------------------|--------------|------------|----------|
| Ambati 2021 [33]                                            | Diffuse STE | Y                            | Normal                    | N/A          | NSAIDs     | Resolved |
| Fleming-Nouri 2021 [34]                                     | STE         | Y                            | mildly decreased left ventricular systolic function | Generalized edema, hyperemia, fibrosis | NSAIDs, IVIG | Resolved |
| Sakaguchi 2021 [35]                                         | Normal      | Y                            | Normal                    | Diffuse myocardial edema | Aspirin, diuretics | Resolved |
| Chen 2021 [36]                                              | Poor R wave progression | Y | N/A | Myocardial fibrosis and edema | NSAIDs | Resolved |
| Das 2021 [37]                                               | STE         | Y                            | Mild LV systolic dysfunction, EF 48% | Myocardial edema | NSAIDS | Resolved |
| Nygaard 2022 [38]                                           | STE         | Y                            | Normal                    | Myocarditis | Ketorolac, colchicine, NSAIDs | Resolved |
| Bartlett 2021 [39]                                          | STE Diffuse | Y | Normal, some reduced LVEF | None | Colchicine, NSAIDs | Resolved |
| Badshah 2021 [40]                                           | Normal      | Y                            | LVEF 45%                  | Edema, pericarditis | Steroid, colchicine, aspirin | Resolved |
| Hung 2022 [41]                                              | STE         | Y                            | Normal                    | Myopericarditis | IVIG, NSAIDs | Resolved |
| McLean 2021 [42]                                            | STE         | Y                            | Pericardial effusion      | Myocardial fibrosis, hyperemia, small pericardial effusion | NSAIDs | Resolved |
| Schauer 2021 [43]                                           | STE         | Y                            | Normal                    | Edema | Supportive only | Resolved |
| Farooq 2022 [44]                                            | Normal      | Y                            | N/A                       | Mild fibrosis of the basal septum and inferior and lateral walls, No myocardial inflammation or infarction | IV and oral steroids | Resolved |
| Umei 2021 [45]                                              | T-wave inversion | Y | Regional hypokinesis | Myopericarditis | None | Resolved |
| Kim 2021 [46]                                               | STE         | Y                            | Normal, small pericardial effusion | Myopericarditis | NSAIDs | Resolved |
| Ameratunga 2022 [47]                                        | Normal      | Y                            | N/A                       | N/A          | None       | Died     |
| Ashaari 2021 [48]                                           | None        | Y                            | N/A                       | No findings  | NSAIDs     | Resolved |
| D’Angelo 2021 [49]                                          | STE         | Y                            | Pericardial effusion      | Myopericarditis | NSAIDs, IVIG, steroids | Resolved |
| Marshall, 2021 [50]                                         | STE V2-V4   | Y                            | Mild pericardial effusion, wall motion abnormality | Myocardial necrosis, diffuse fibrosis | NSAIDs | Resolved |
| Facetti, 2021 [51]                                          | STE         | Y                            | N/A                       | Myopericarditis | NSAIDs | Resolved |
| King 2021 [52]                                              | TWI lateral waves, STE | Y | Normal | Myopericarditis | None | Resolved |
| Hasnie 2021 [53]                                            | Diffuse STE | Y                            | Normal                    | Myopericarditis | Aspirin, colchicine | Resolved |
| Patrignani 2021 [54]                                        | Normal      | Y                            | Hypokinetic mid to apical anterior segments | Myocarditis | None | Resolved |
of patients (16%), intravenous immunoglobulin (IVIG) was also utilized in addition to NSAIDs and steroids, particularly in younger patients. In cases where follow-up was available, a complete clinical resolution was documented in 87 (99%) patients during the follow-up. There was only one recorded death among all reviewed cases.

Overall, patients presenting with the symptoms concerning myopericarditis require cautious triaging whether they are seen in the ambulatory or emergency department setting. The American Heart Association recommends that patients seek immediate medical advice if they experience sudden, sharp, stabbing chest pain, shortness of breath, or loss of consciousness [57]. The usual workup involves a careful history and physical exam, ECG, cardiac enzymes, and PCR for common viral etiologies when indicated. Even though elevated troponin may indicate acute cardiac injury, it is not specific to myocarditis. This is important as it may mimic other cardiac disorders and therefore requires a high level of clinical suspicion. The utility of CMR in this patient population remains unclear, but it may offer a further cardiac evaluation to confirm the diagnosis or better characterize progression or resolution [58]. There are no guidelines available for managing COVID19VAM or COVID19VAP. However, the treatment usually involves NSAIDs, colchicine, and guideline-directed therapy for heart failure with a reduced ejection fraction. Steroids and IVIG have immunomodulatory properties, theoretically reducing the specific immune response triggered by the administration of the COVID-19 vaccine. However, steroids and IVIG use should be limited to refractory cases as only limited data is available.

Majority of patients with myocardial and pericardial inflammation after the COVID-19 vaccine show complete resolution. A three-month follow-up of five patients with myocarditis after COVID19 vaccination showed normalization of ejection fraction and resolution of myocardial edema in all patients [58]. However, at this point, there remains a scarcity of long-term data for COVID-19 vaccine–related inflammatory heart conditions.

**Activity Restriction and Return to Play for Athletes**

**COVID-19 Infection–Related Myocarditis**

The prevalence of COVID-19 infection–related myocarditis is up to 3% in young athletes (Big Ten COVID-19 Registry). There was no adverse cardiac event in short-term surveillance of COVID-19-positive athletes with myocarditis [59]. American College of Cardiology Guideline recommends at least 3–6 months of exercise abstinence in athletes diagnosed with myocarditis after a COVID-19 infection. An expert evaluation and testing is indicated in these athletes prior to resuming the training and exercise. In selected cases of rapid resolution of symptoms, earlier re-evaluation may also be sought prior to 3 months (not sooner than 1 month) [60•]. There is a need for more studies in this arena to understand the disease progression and resolution of myocarditis with long-term effects.

**COVID-19 Vaccine–Related Myocarditis**

The burden of COVID-19 vaccine–related cardiac inflammatory conditions is not specifically reported for athletes. The data from the US Military Health System showed only 23 cases (median age 25 years) after 2.8 million doses of mRNA vaccinations [61]. A case of myocarditis in an athlete who presented with squeezing chest pain 10 days after the second dose of mRNA vaccine was identified. He was managed with ibuprofen and beta blocker and athletic activity was restricted for 3–6 months [62]. Screening for myocarditis is not indicated in asymptomatic athletes who received COVID-19 vaccination. Activity restriction along with repeat testing in select cases is recommended in athletes developing this extremely rare vaccine-related myocarditis [60•].

**COVID-19 Infection and COVID-19 Vaccine–Related Pericarditis**

There is paucity of data for physical activity in patients developing pericardial inflammation secondary to COVID-19 infection or COVID-19 vaccine. In general, patients with pericarditis are recommended to limit the physical activity as activity has anecdotally been related to increased severity and recurrence of pericarditis [63, 64].

**Recommendations for COVID-19 Vaccination**

The absolute number of myocarditis events is 1–10 per million vaccinated persons following the COVID-19 vaccine. However, the risk of myocarditis is significantly high after a COVID-19 infection (40 per million) [65]. Additionally, COVID-19 infection–related myocarditis is found in around 2 to 4 patients hospitalized for COVID-19 per 1000 hospitalizations as compared to 10 cases of vaccine-related myocarditis per 100,000 vaccinations [66]. Similarly, higher rates are reported for pericarditis and myopericarditis in COVID-19 infection as compared to COVID-19 vaccines [65, 67••]. There was no increase in the recurrence of pericarditis after COVID19 vaccination in patients on rilonacept therapy [68].

The most common age group affected by COVID19VAM and COVID19VAP is adolescent boys (between 12 and 17 years). A study estimated substantially low incidence rates in milder complications and improved outcomes for mortality...
and hospitalizations within this age group [69]. The current data suggests that the risk of inflammatory cardiac conditions, although rare overall, is significantly higher in COVID-19 infection as compared to COVID-19 vaccines. The benefit of vaccination clearly outweighs the risk of these rare side effects. Therefore, COVID-19 vaccination is still recommended in all age groups for the benefits of preventing hospitalizations and severe COVID-19 infection sequela.

Conclusions and Future Directions

Pericardial and myocardial inflammation is a rare side effect of the COVID-19 vaccine that resolves with anti-inflammatory medications. Mechanisms of vaccine-induced inflammatory heart conditions and the long-term effect of these inflammatory conditions need exploration. Moreover, further studies are required to comparatively assess the COVID-19 infection and COVID-19 vaccine–related inflammatory heart conditions.

Declarations

Conflict of Interest Dr. Klein has received a research grant from and is a scientific advisory board member for Kiniksa Pharmaceuticals; and is a scientific advisory board member for Swedish Orphan Biovitrum, Sweden, Pfizer, USA, and Cardioli Therapeutics; and he has a leadership or fiduciary role on the National Board of Echocardiography. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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