Review

Cardiopulmonary Effects of COVID-19 Vaccination: A Comprehensive Narrative Review

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Review

Cardiopulmonary Effects of COVID-19 Vaccination: A Comprehensive Narrative Review

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Abstract: Coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccines have been associated with numerous side effects since widespread release to the public. Cardiovascular complications include myocarditis and pericarditis, Takotsubo cardiomyopathy, postural orthostatic tachycardia syndrome (POTS), arrhythmias, sudden cardiac death, and cardiac tamponade. Pulmonary complications are pulmonary embolism (PE), interstitial lung disease (ILD), idiopathic pulmonary fibrosis (IPF), pneumonia, eosinophilic granulomatosis with polyangiitis, pneumonitis, and pulmonary hypertension. Despite these complications, the risk-benefit analysis still strongly favors vaccination, as these events occur more frequently with natural infection and confer a significantly worse prognosis. This study outlines the evidence surrounding each attributed effect, the clinical course including diagnosis and management, and the proposed pathophysiology. To our knowledge, this is the most comprehensive review of the cardiopulmonary effects of COVID-19 vaccination to date.

Keywords: cardiovascular; pulmonary; covid-19 vaccine

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for the coronavirus disease 2019 (COVID-19) global pandemic, which has hundreds of millions of infections and millions of fatalities to date [1]. In the early stages of the pandemic, widespread lockdowns were thought to be the only defense against the virus. Towards the end of 2020, this changed with the United States Food and Drug Administration's emergency approval of two messenger RNA (mRNA) vaccines: Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-1273. Clinical trials for both vaccines showed 94-95% efficacy in preventing infection with self-limiting local and systemic side effects, such as low-grade fever, injection site pain, fatigue, and headache [2,3].

COVID-19 mRNA vaccines contain nucleoside-modified messenger RNA (mRNA), encoding the SARS-CoV-2 spike glycoprotein, encapsulated in lipid nanoparticles [4]. Cells then produce the viral spike protein, which induces an adaptive immune response [4]. Resultant spike-protein IgG antibodies prevent viral attachment to angiotensin-converting enzyme 2 (ACE2) receptors on the host cell, thereby inhibiting entry and neutralizing the virus [4]. Alongside the production of these antibodies is a significant inflammatory response via cytokine activation [1]. This inflammatory response leads to the local and systemic side effects attributed to these vaccines.

Although only mild side effects were noted in the mRNA vaccine trials, reports of more serious adverse events began to surface following their widespread use amongst the public. This study will focus on some of the cardiopulmonary effects attributed to COVID-19 vaccination. We will outline

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the evidence surrounding each attributed effect, the clinical course including diagnosis and management, and the proposed pathophysiology.

2. Cardiovascular Effects of COVID-19 Vaccination

2.1. Myocarditis and Pericarditis

Myocarditis and pericarditis are the most notorious and extensively studied cardiovascular effects associated with COVID-19 vaccines, particularly mRNA vaccines such as the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna). The risk of myocarditis from these mRNA vaccines has been estimated at 4-28 cases per 100,000 doses, with increased risk seen in males, people under 30 years old, and after the second dose [5]. However, the true incidence is unknown given the lack of a centralized reporting system worldwide. Notably, the risk of myocarditis following COVID-19 vaccination is less than that conferred through natural infection, with a recent meta-analysis estimating the incidences at 19.7 per 1,000,000 and 2.76 per 1000, respectively [6].

Patients with COVID-19 vaccination-associated myo-/pericarditis typically present three days following vaccination with chest pain, fever, and dyspnea being the most prevalent symptoms [5,7]. Common laboratory findings include elevated troponin, B-type natriuretic peptide (BNP), and inflammatory markers, such as c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [7]. Electrocardiogram (EKG) abnormalities are seen in 80-90% of cases with ST elevations, sinus tachycardia, and nonspecific ST-segment and T-wave changes being the most common [5,7,8]. Echocardiogram (ECHO) findings include left ventricular ejection fraction (LVEF) below 50% in anywhere from 21-44% of cases, while pericardial effusions are seen approximately 20% of the time [5,7,8]. Definitive diagnosis of myo-/pericarditis is achieved either through cardiac magnetic resonance imaging (cMRI), which would show late gadolinium enhancement corresponding to myo- or pericardial inflammation, or through cardiac biopsy, which is utilized less frequency due to its invasive nature [7,8].

Treatment of this phenomenon is typically supportive with anti-inflammatories, such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, colchicine, and steroids [7,8]. Guideline-directed medical therapy with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and diuretics are also frequently used, particularly in cases with reduced LVEF [8]. Fortunately, myo-/pericarditis associated with COVID-19 vaccination has a favorable prognosis with resolution of symptoms in most cases and median hospitalizations around 3-5 days [7,8]. However, one study of 182 patients noted that 3 cases (1.6%) resulted in death, so severe adverse outcomes are possible [8]. Additionally, persistently reduced LVEF can be seen in around 10% of cases, while ongoing symptoms have been seen in as many as 12% of cases [5]. Furthermore, persistent abnormalities on cMRI are seen in around 50% of cases at a median follow-up time of 6-7 months [5]. In comparison to myo-/pericarditis from natural COVID-19 infection, vaccine-associated cases appear to have a more benign disease course with less need for invasive treatment, increased rates of LVEF recovery to baseline, and significantly fewer mortalities [5,7].

Despite its well-documented nature, the underlying mechanism behind this association is still a topic of debate. Hypotheses include activation of the immune system, hypersensitivity reactions, and molecular mimicry [9]. Activation of the innate and adaptive immune systems occurs in response to either the spike glycoprotein or the mRNA itself, resulting in cardiac inflammation through upregulation of pro-inflammatory pathways and cytokines [5,9]. Hypersensitivity reactions are also possible as a result of an immune response to the other components of the vaccine, such as the lipid nanoparticle, whose ionizable lipids can activate toll-like receptors and lead to myocarditis [5]. Furthermore, molecular mimicry can occur when antibodies against the spike protein cross-react with cardiac self-antigens, such as myosin heavy chains or troponin C1, causing inflammation [4,5]. Additionally, higher levels of androgens may enhance the pro-inflammatory responses of the immune system, while estrogen exhibits an anti-inflammatory effect, highlighting a possible explanation for why this phenomenon is seen more frequently in males [4,5].

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2.2. Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy (TCM), also known as broken heart syndrome and stress-induced cardiomyopathy, has increased in prevalence since the start of the COVID-19 pandemic, being attributed to both natural infection and vaccines [10]. TCM is characterized by a transient left ventricular dysfunction which is often precipitated by emotional or physical stress. Although the pathophysiology is not entirely understood, multiple hypotheses surrounding TCM from COVID-19 vaccination exist. One hypothesis suggests myocardial stunning from microvessel or multi-vessel vasospasm and direct myocardial injury in response to elevated catecholamine levels seen during stress [11]. Another involves elevated pro-inflammatory cytokines, as seen following vaccination, causing this phenomenon [11]. Furthermore, the interaction between spike proteins and ACE2 receptors may cause a relative overactivity of the pro-inflammatory angiotensin II [11].

TCM following COVID-19 vaccination tends to occur in older females, with systematic reviews yielding a median age of 61.5 years and female predominance as high as 75-90% [11,12]. Patients typically present 2-3 days following vaccination with chest pain and dyspnea, while hospitalization lasts an average of 7-10 days [11,12]. Elevated troponin and abnormal EKG findings are seen in all patients, while ECHO findings are variable with reduced LVEF seen in anywhere from 10-90% of patients [11,12]. Although there are no guidelines or protocol, treatment typically includes heart failure medications, such as ACE inhibitors or ARBs and beta-blockers [10]. Mortality and recurrence rates are estimated at 3.5-10.6% and 2-11%, respectively [10].

2.3. Postural Orthostatic Tachycardia Syndrome (POTS)

Postural orthostatic tachycardia syndrome (POTS) is a form of dysautonomia that has been linked to COVID-19 vaccinations, although the odds of development are 1.52-2.12 times more likely from natural infection [13,14]. POTS is characterized by an excessive heart rate increase after standing, with associated dizziness, fatigue, and palpitations [15]. Demographics of patients developing POTS following COVID-19 vaccination are 59% female with a mean age of 56, with 67% Caucasian, 12% Hispanic, 11% African American, and 9% Asian [13]. Patients typically present within a few days of vaccination and the diagnosis is clinical, although elevated norepinephrine levels, reduced heart rate variability, and a positive tilt table test can be seen [15]. Treatment typically involves lifestyle modifications, such as increased fluid and salt intake, exercise, and compression stockings, although pharmacological therapy with ivabradine, corticosteroids, and beta-blockers, amongst other medications, can also be tried [15]. Studies have shown that symptoms could persist for months in some cases, especially in patients with a history of autonomic dysfunction [16]. Possible mechanisms surrounding this association include immune-mediated transient autonomic dysfunction, molecular mimicry between vaccine antigens and autonomic pathways, or dysautonomia from vaccine-induced inflammation, similar to the mechanism underlying post-viral autonomic syndromes [15].

2.4. Arrhythmias

Arrhythmias, ranging from benign palpitations to life-threatening conditions, have been reported following COVID-19 vaccination. A large meta-analysis determined an incidence of 22 per 10,000 people following the Pfizer vaccine and 76 per 10,000 following Moderna [17]. Both bradyarrhythmias and tachyarrhythmias have been observed. Complete AV block has been reported after patients presented with syncope and dizziness within a few weeks of COVID-19 vaccination, with treatment via pacemaker insertion [18]. Tachyarrhythmias include atrial fibrillation (AF) and other supraventricular tachycardias, ventricular tachycardia (VT), and ventricular fibrillation (VF). Atrial fibrillation has been observed at an incidence of 5 per million doses of COVID-19 vaccine, particularly in older adults or those with prior cardiovascular comorbidities, with patients presenting within a week or two of vaccination [19]. COVID-19 vaccination has also been implicated in unmasking Brugada in genetically predisposed individuals, due to fever-induced sodium channel

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dysfunction, and presenting as VT [20–22]. Similarly, vaccination can unmask underlying Long QT syndrome and present as syncope with VT [23,24]. Additionally, isolated cases of VT and VF following vaccination have been documented, often in individuals with underlying structural heart disease or concomitant myocarditis [25,26]. Treatment and prognosis are arrhythmia-specific, as are proposed mechanisms. In short, bradyarrhythmias are attributed to the humoral response from COVID-19 vaccinations inducing conduction system abnormalities, atrial tachycardias are felt to be from underlying pro-inflammatory cytokines and molecular mimicry, while ventricular tachycardias are associated with myocardial edema and ischemia [18].

2.5. Sudden Cardiac Death

Sudden cardiac death (SCD) is an exceptionally rare but devastating adverse event reported following COVID-19 vaccination [27]. Most documented cases have been associated with myocarditis or undiagnosed pre-existing cardiac conditions, both of which lead to fatal arrhythmias [27,28]. Mechanistically, SCD may result from the similar mechanisms mentioned before. Autopsy findings in reported cases frequently reveal significant inflammatory infiltration of myocardial tissue, consistent with vaccine-associated myocarditis [29]. The temporal and disclaimed association between COVID-19 vaccination and SCD often ranges from days to a few weeks after the administration, stressing the need for an increased clinical vigilance in populations already at risk [30]. For example, individuals with predisposing factors such as prior myocarditis, genetic arrhythmia syndromes, or significant structural heart disease may require careful monitoring. Despite being such a rare adverse event, SCD has profound and serious implications which emphasizes the importance of balancing the benefits of vaccination against these minimal risks and tailoring recommendations for high-risk groups. Detailed case reports have highlighted the importance of early recognition of warning signs such as chest pain and syncope, which could precede fatal outcomes [31].

2.6. Cardiac Tamponade

Cardiac tamponade has also been reported in very few isolated cases following COVID-19 vaccination [32,33]. In these reports, patients often present with dyspnea, hypotension, and jugular venous distension within days to weeks of vaccination. The condition can arise secondary to severe pericarditis or as part of a broader inflammatory response [34]. Echocardiographic findings typically show a pericardial effusion with some evidence of hemodynamic compromise such as a right atrial, a right ventricular diastolic collapse or microthrombi formation [32,35]. After an intervention-guided pericardiocentesis reports have noted inflammatory exudates suggestive of immune-mediated pericardial injury [32]. Emerging reports suggest that persistent effusions may occur in rare cases, needing repeated interventions and long-term anti-inflammatory therapy [35]. Recognizing at-risk individuals, particularly those with pre-existing pericardial conditions, is crucial for well-timed management.

2.7. Other Reported Cardiovascular Events

In addition to the conditions described above, there are other rare cardiac events that have been associated with COVID-19 vaccination. Acute coronary syndrome (ACS) has been reported in individuals with predisposing risk factors, likely triggered by heightened inflammatory states post-vaccination [36]. Hypertensive crises and exacerbation of pre-existing cardiac conditions, such as heart failure and atrial fibrillation, have also been noted in temporal association with the vaccination [37]. Importantly, differentiating these events from just merely coincidental occasions is important, given the large number of people receiving the vaccine worldwide.

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2.8. Comparative Risk Analysis

When considering the pros and cons in terms of the cardiovascular effects of COVID-19 vaccination, it is important to compare these risks with the cardiovascular complications of the natural SARS-CoV-2 infection. As alluded to above, natural COVID-19 infection has been associated with a substantially higher risk of myocarditis, arrhythmias, thromboembolic events, and other cardiac complications [38,39]. It is also known that vaccination significantly reduces the risk of severe disease, which includes these potentially life-threatening cardiovascular outcomes mentioned [40]. Furthermore, complication of natural infection with these cardiovascular events confers a significantly worse prognosis. Public health efforts should emphasize the relative rarity of vaccine-associated events in contrast to the documented burden of cardiovascular sequelae from COVID-19.

3. Pulmonary Effects of COVID-19 Vaccination

3.1. Pulmonary Embolism

Although vaccine-induced thrombosis and thrombocytopenia (VITT) is a rare complication primarily linked to adenoviral vector vaccines, cases of pulmonary embolism (PE) have also been documented following mRNA COVID-19 vaccination [41]. A systematic review identified 301 cases of PE among 17,636 cardiovascular events reported after mRNA vaccination [42]. Similarly, another study found that while the risk of adverse events post-mRNA vaccination remains low, PE and deep vein thrombosis (DVT) were among the most frequently reported thrombotic complications [43]. Numerous case reports exist documenting this phenomenon, typically days to weeks following vaccination, and often in individuals with no prior thrombotic risk factors [44–48].

COVID vaccine-associated PE typically presents with dyspnea, chest pain, and palpitations, but cough and syncope have also been reported [44,47]. Cardiac arrest requiring resuscitation is a feared complication reported in some case reports [45,47]. Diagnosis is established primarily through computed tomography (CT) pulmonary angiography, which shows clot burden in the pulmonary arteries [45,46]. Cardiac imaging findings include right ventricular dilation and pulmonary hypertension [46]. Elevated c-reactive protein (CRP) levels can also be seen, highlighting underlying inflammation [45,46,48]. Treatment consists predominantly of thrombolytic therapy, low-molecular-weight heparin (LWMH), and Factor Xa inhibitors, such as apixaban and rivaroxaban, leading to favorable outcomes in most cases [44–47]. However, persistent pulmonary hypertension and right heart strain can be seen in some patients [46]. Furthermore, patients with pre-existing pulmonary disease may experience severe complications, including respiratory failure and mortality [48].

The pathophysiology of vaccine-associated PE remains unclear. Proposed mechanisms include platelet factor 4 (PF4) activation, leading to a hypercoagulable state similar to VITT [49]. Another hypothesis is cytokine-induced systemic inflammation causing concomitant endothelial damage and prothrombotic state, which predisposes to thrombosis formation with embolic travel to the pulmonary vasculature [48]. Future studies into this phenomenon are needed to further elucidate the true mechanism and determine whether causation exists between COVID-19 vaccines and thrombotic events.

3.2. Interstitial Lung Disease

Interstitial lung disease (ILD) has emerged as a rare but notable pulmonary complication following COVID-19 vaccination, with several studies evaluating the incidence, potential mechanisms, and clinical outcomes associated with vaccine-related ILD exacerbations. While large-scale analyses have not demonstrated a statistically significant increased risk of ILD following vaccination, isolated case reports and retrospective studies suggest that certain subgroups, particularly those with pre-existing autoimmune-related ILD could be at a higher risk for exacerbations. A retrospective study of 545 ILD patients found that 17 individuals (3.1%) experienced worsening respiratory symptoms following COVID-19 vaccination, with 4 cases (0.7%) meeting

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criteria for acute exacerbations of ILD (AE-ILD) requiring hospitalization [50]. Further large-scale disproportionality analysis using VigiBase, a global pharmacovigilance database, identified 679 cases of ILD among 1,233,969 vaccine-related reports, predominantly linked to mRNA vaccines such as Pfizer-BioNTech (55.4%) and Moderna (11.5%) [51]. These cases were managed with steroid pulse therapy, with two patients needing additional immunosuppressive treatment with IV cyclophosphamide [50]. Although AE-ILD post-vaccination is rare, vigilance is necessary, particularly in patients with autoimmune-related ILD. Drug-induced ILD (DI-ILD) has also been reported following COVID-19 vaccination, with cases presenting with acute respiratory failure, hypoxemia, and extensive ground-glass opacities on imaging [52]. Two cases of DI-ILD involved elderly male patients developing acute respiratory distress within days of vaccination, with laboratory findings of elevated pulmonary injury markers and inflammatory cytokines [52]. Both cases demonstrated clinical improvement following corticosteroid therapy, reinforcing the importance of early recognition and intervention [52].

The immunopathogenesis underlying vaccine-associated ILD remains speculative, with many different proposed mechanisms. One mechanism involves exaggerated immune activation through cytokine release, particularly interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), which could lead to alveolar inflammation [53]. Additionally, mRNA vaccine-induced Th1-cell responses may promote macrophage activation, exacerbating pre-existing pulmonary fibrosis [53]. Vaccine adjuvants have also been implicated in immune dysregulation, potentially triggering inflammatory cascades leading to pneumonitis or fibrotic lung injury [53]. Further research into this pathophysiology is warranted to further the risk-benefit analysis of vaccination in this population.

Despite these concerns, emerging evidence suggests that COVID-19 vaccination may not only be safe for ILD patients but may also confer a protective effect against ILD development. A retrospective cohort study utilizing a Korean national database analyzed over 1.1 million matched individuals and found a significantly lower incidence of ILD among vaccinated individuals compared to their unvaccinated counterparts [54]. The incidence rate was 6.8 per 10,000 person-years in the vaccinated group versus 10.6 per 10,000 in the unvaccinated group ($p < 0.0001$), suggesting that COVID-19 vaccination may reduce the overall burden of ILD at the population level [54].

3.3. Idiopathic Pulmonary Fibrosis

As with ILD, COVID-19 vaccination has been associated with acute exacerbations of idiopathic pulmonary fibrosis (IPF). One study on IPF patients admitted for respiratory deterioration had 10 diagnosed with acute exacerbations of IPF (AE-IPF) and four of those patients (40%) had received the Pfizer-BioNTech vaccine within the preceding three to five days [55]. Notably, two of these patients ultimately succumbed to their exacerbations [55]. However, the rest of the associations come primarily through case reports. One case involved an 82-year-old man who, after remaining asymptomatic, developed progressive dyspnea, cough, and anorexia 1.5 months post-vaccination [56]. Another case documented an 84-year-old male with fibrotic ILD who developed AE-IPF within nine days of receiving the second dose of the Pfizer-BioNTech vaccine [57]. A third case involved a 72-year-old male with a well-documented history of IPF who presented with respiratory decline one-week post-vaccination [58]. Diagnosis is obtained using high-resolution computed tomography (HRCT), which reveals new ground-glass opacities and honeycombing, and through bronchoscopy [56,57]. High-dose corticosteroid therapy resulted in improvement in symptoms for all patients in these case reports [56–58]. Despite these concerns, COVID-19 vaccination in patients with chronic lung disease to protect from severe infection is felt to outweigh the risks, but there is need for careful post-vaccination monitoring for acute exacerbations in IPF patients [59].

While causality remains unproven, several mechanisms have been proposed to explain the potential link between COVID-19 vaccination and AE-IPF. Vaccine-induced immune activation may worsen pulmonary fibrosis through excessive Th1-mediated inflammation and cytokine release [55]. The upregulation of IL-6 and IL-22 observed in IPF patients post-vaccination suggests a persistent

 doi:10.20944/preprints202504.0735.v1

pro-fibrotic environment, which could heighten susceptibility to disease exacerbation [55]. Additionally, alterations in immune cell populations, particularly the increase in regulatory T cells and cytotoxic lymphocytes, may play a role in modulating immune responses in a way that predisposes certain individuals to AE-IPF following vaccination [55].

3.4. Pneumonia

Pneumonia, both as a direct inflammatory reaction and as a complication of preexisting interstitial lung disease, has been reported in association with COVID-19 vaccination. A case of concurrent acute exacerbation of idiopathic nonspecific interstitial pneumonia (iNSIP) and pulmonary embolism was reported in an 82-year-old woman who had been clinically stable for three years before developing acute dyspnea two days after receiving a booster dose of the Pfizer-BioNTech (BNT162b2) vaccine [48]. Despite initial management, her respiratory failure worsened, eventually leading to hemodynamic instability, multiorgan failure, and death [48]. Cases of organizing pneumonia following COVID-19 vaccination have also been reported, with patients presenting with cough, dyspnea, and fever [60,61]. Two additional cases of acute exacerbation of interstitial pneumonia following mRNA COVID-19 vaccination have been reported [62]. In the first case, an 83-year-old man with stable idiopathic interstitial pneumonia developed high fever and dyspnea one day after receiving his first Pfizer-BioNTech vaccine dose [62]. CT imaging revealed newly developed diffuse ground-glass opacities, and laboratory tests showed elevated CRP and surfactant protein-D (SP-D), both markers of pulmonary inflammation [62]. He was treated with corticosteroid pulse therapy, leading to gradual improvement [62]. In the second case, a 65-year-old man with a history of acute exacerbation of interstitial pneumonia, previously treated with steroids, developed low-grade fever and dyspnea six days after receiving his second Pfizer-BioNTech vaccine dose [62]. CT imaging revealed ground-glass opacities with traction bronchiectasis, while blood tests showed severe anemia, leukopenia, and elevated CRP and SP-D [62].

Mechanisms underlying vaccine-related pneumonia is not completely understood. Vaccine-induced immune activation may play a role through excessive Th1-mediated inflammation and cytokine release, leading to increased IL-6 and tumor TNF-α production, which are known mediators of lung injury [62]. Additionally, molecular mimicry between vaccine antigens and pulmonary self-antigens could theoretically contribute to autoimmune-like reactions, particularly in patients with preexisting ILD or immune dysregulation [62]. Similar underlying cytokine storm reactions have been linked to severe complications from natural COVID-19 infections, which typically have a worse prognosis than its vaccine counterparts [48].

3.5. Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis, formerly known as Churg-Strauss syndrome, is a rare systemic vasculitis characterized by eosinophilic inflammation, asthma, and multiorgan involvement [63] It is part of the spectrum of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides and is thought to result from immune dysregulation leading to excessive eosinophilic activation and vascular inflammation [63]. Several cases of new-onset EGPA and related vasculitides, including granulomatosis with polyangiitis (GPA), have been reported following COVID-19 mRNA vaccination, raising concerns about potential vaccine-induced immune activation in predisposed individuals.

Case reports documenting this highlight patients presenting with a variety of nonspecific symptoms, such as low-grade fever, edema, myalgias, nasal congestion, and rash 2-15 days following COVID-19 vaccination [64–68]. Laboratory findings include severe eosinophilia, elevated inflammatory markers, and elevated myeloperoxidase (MPO) antibodies [64–66,68]. Treatment is primarily corticosteroids and cyclophosphamide for more severe cases, while plasmapheresis, rituximab, and tumor necrosis factor (TNF) inhibitors can be used for refractory disease [63].

Cases of new-onset EGPA and GPA following COVID-19 vaccination raises important questions about the underlying immunological mechanisms. Several potential explanations have been

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proposed, including molecular mimicry, bystander activation, and immune system priming [64–67]. Molecular mimicry occurs when vaccine components resemble self-antigens, triggering an autoimmune response [64,65]. Bystander activation involves excessive immune stimulation leading to collateral tissue damage [64]. The presence of ANCA antibodies in multiple post-vaccination cases suggests that the vaccine may trigger an underlying immune response leading to EGPA in predisposed individuals [66].

3.6. Pneumonitis

Pneumonitis is non-infectious inflammatory reaction of the lung parenchyma and has been reported in rare cases following COVID-19 vaccination. A large-scale nationwide multicenter survey conducted in South Korea identified 49 cases of COVID-19 vaccine-associated pneumonitis, occurring within a few weeks of vaccination [69]. Median age of affected individuals was 66 years, with a predominance of male patients (61%) [69]. Most cases were associated with mRNA vaccines, with the Pfizer-BioNTech BNT162b2 vaccine accounting for 57% and the Moderna mRNA-1273 vaccine for 35% [69]. Most common presenting symptoms included dyspnea (87%), cough (67%), and fever (37%) [69]. HRCT scans revealed bilateral ground-glass opacities in 85% of cases, as well as interstitial infiltrates and consolidations [69]. Pulmonary function tests demonstrated a restrictive ventilatory pattern with reduced diffusion capacity for carbon monoxide, indicating impaired gas exchange [69]. Bronchoalveolar lavage analysis revealed lymphocytic alveolitis, supporting an immune-mediated pathogenesis [69]. Treatment was primarily systemic corticosteroids and, despite therapy, four patients (9%) required mechanical ventilation and eight (17%) succumbed to their illness [69]. These findings show the potential severity of vaccine-associated pneumonitis.

Another distinct form of vaccine-related pneumonitis is radiation recall pneumonitis (RRP), a rare inflammatory reaction occurring within previously irradiated lung tissue following exposure to triggering agents such as chemotherapy, immunotherapy, or vaccines [70]. A case of RRP was reported in a 48-year-old male with locally advanced unresectable non-small-cell lung cancer, who had undergone prior chemoradiotherapy and maintenance therapy with durvalumab [70]. He received his first dose of the Pfizer-BioNTech vaccine eight days after his last durvalumab infusion and the second dose 21 days later [70]. He developed a fever and dry cough 19 days after the second dose of vaccine and a CT scan showed new infiltrates consistent with RRP [70].

The underlying mechanisms linking COVID-19 vaccination to pneumonitis are not yet fully understood, but several hypotheses have been proposed. Vaccine-induced immune activation may provoke excessive inflammatory responses in susceptible individuals, particularly those with preexisting ILD or prior lung-directed therapies [69]. Molecular mimicry between vaccine components and lung-specific antigens could potentially trigger an autoimmune reaction, leading to pulmonary inflammation [69]. Additionally, mRNA vaccines have been shown to induce robust cytokine responses, which may contribute to immune-mediated lung injury in predisposed individuals [69]. Similarly, RRP is felt to arise from the vaccine-induced inflammatory response within previously irradiated lung tissue [70].

3.7. Pulmonary Hypertension

Pulmonary hypertension following COVID-19 vaccination has been reported in a few case reports. Patients typically present with dyspnea and fatigue within days to weeks following vaccination [71–73]. Some cases are associated with concomitant pulmonary embolism [71,73]. Echocardiography can suggest pulmonary hypertension and note right heart strain, but definitive diagnosis requires right heart catheterization [71–73]. Prognosis is typically poor with permanent organ damage and/or death being common [72,73].

Potential mechanisms linking COVID-19 vaccination to PH remain speculative but include endothelial dysfunction, microvascular thrombosis, and immune-mediated vascular remodeling [71–73]. The spike protein encoded by mRNA vaccines has been shown to interact with endothelial cells, leading to increased expression of inflammatory cytokines, endothelial activation, and a

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prothrombotic state [71,72]. In predisposed individuals, these changes may contribute to vascular remodeling and increased pulmonary vascular resistance, ultimately resulting in PH [73]. In cases involving microvascular thrombosis, as suggested by elevated D-dimer levels, the immune response to vaccination may trigger localized clot formation, leading to impaired pulmonary circulation and increased pulmonary pressures [71,73].

3.8. Comparative Risk Analysis

As with the cardiovascular complications of COVID-19 vaccination, comparison of the risks of these pulmonary effects from natural infection is important. While thromboembolic events with vaccination is rare, a large meta-analysis found the rates of DVT and PE from natural infection to be 12.1% and 7.1%, respectively [74]. Furthermore, despite the slight increases in risk of acute exacerbations of ILD and IPF, the benefit that vaccination provides for those with already compromised lungs is invaluable. Additionally, although pneumonia following vaccination is exceedingly rare, serious complications of natural COVID-19 infection, such as COVID pneumonia, occurs in approximately 15% of patients [75]. All this evidence supports the benefit of vaccination, as the associated complications occur more readily with natural infection.

4. Conclusions

To our knowledge, this is the most comprehensive review of the cardiopulmonary effects of COVID-19 vaccination to date. Cardiovascular complications examined include myocarditis and pericarditis, Takotsubo cardiomyopathy, postural orthostatic tachycardia syndrome (POTS), arrhythmias, sudden cardiac death, and cardiac tamponade. Pulmonary complications examined are pulmonary embolism (PE), interstitial lung disease (ILD), idiopathic pulmonary fibrosis (IPF), pneumonia, eosinophilic granulomatosis with polyangiitis, pneumonitis, and pulmonary hypertension. Despite these complications, the risk-benefit analysis still strongly favors vaccination, as these events occur more frequently with natural infection and confer a significantly worse prognosis.

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