Cardiovascular Concerns from COVID-19 in Pilots

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BACKGROUND: Cardiovascular disease, now complicated by the COVID-19 pandemic, remains a leading cause of death and risk for sudden incapacitation for pilots during flight. The capacity for aeromedically significant cardiovascular sequelae with potentially imperceptible clinical symptoms elicits concern both during and following resolution of acute COVID-19 in pilots.

OBJECTIVE: We summarize the current state of knowledge regarding COVID-19 cardiovascular implications as applied to the aviation environment to better understand their significance toward flight safety and application toward a focused cardiovascular screening protocol following recovery from infection.

METHODS: A narrative review of the cardiovascular implications of COVID-19 infection was performed using the PubMed literature search engine and existing organizational guidelines. In addition, to established medical aviation benchmarks, surrogate populations examined included high performance athletes (as a correlate for high G-forces), and scuba divers (as an environmental work analog). Conditions of primary concern included myocardial injury, proarrhythmic substrates, risk of sudden death, myopericarditis, pulse orthostatic lability in response to vigorous activity, cardiovagal dysfunction, and thromboembolic disease.

LITERATURE REVIEW: Cardiovascular screening guideline recommendations post-infection recovery are suggested based on profile stratification: airperson flight class, tactical military, and aerobatic pilots. This provides an approach to inform aeromedical decision making.

CONCLUSION: Aviation medical examiners should remain cognizant of the clinically apparent and occult manifestations of cardiovascular dysfunction associated with COVID-19 infection when applying return-to-work screening guidelines. This will ensure high flight safety standards are maintained and sudden incapacitation risk mitigated during and following the ongoing pandemic.

KEYWORDS: cardiovascular; cardiac; heart; cardiovascular screening; cardiac screening; COVID-19 screening: coronavirus; SARS-CoV-2; Coronavirus disease 2019; aviation; airpersons; airmen.

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Worldwide rigorous aeromedical selection screenings must maintain high standards to minimize significant in-flight incapacitation risk, with particular emphasis on cardiovascular disease.[24] Acceptable medical incapacitation combined risk tolerance causing aircraft incidents approximates 1 per 109 flying hours,[67] maintaining the "1% rule per annum risk threshold" industry standard per the International Civil Aviation Organization.[46] Cardiovascular conditions remain a leading cause of groundings, especially in pilot cohorts older than 50 yr of age,[87] presenting aeromedical examiners medical optimization opportunity to reduce medical incapacitation events in allocating special issuances, and medication suitability screenings as approved by the FAA.[28]

Compressed airline passenger transport schedules intuitively can place physiologic stress on commercial pilots. In addition, the added exposures to high G-forces, hypoxic conditions, thermal stresses, and cognitive strain for high-performance pilots have been shown to potentially present inherent occupational cardiovascular risk factors during and

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after flights despite the absence of other contributing elements due to prolonged sympathetic nervous system activation,[36] vagal withdrawal, cardiac baroreflex sensitivity depreciation,[93] and resulting dynamic heart rate variability reductions.[74] Existing predispositions recently have been exacerbated amid the COVID-19 pandemic, posing dilemmas for the ideal cardiovascular medical care approach to these affected patient populations following infection recovery. The capacity for significant cardiovascular sequelae (i.e., malignant arrhythmias, myocardial infarction, myocarditis, pericarditis, sudden cardiac death) with potentially imperceptible clinical symptoms elicits concern both during and after resolution of acute COVID-19 in pilots. Specific medical risk factor evaluations and clinical management considerations warrant deliberation prior to return to aviation duty. Cardiovascular disease, now complicated by the COVID-19 pandemic, remains a leading cause of death and risk for sudden incapacitation for pilots during flight.

We thus comprehensively summarize the current state of knowledge regarding COVID-19 cardiovascular implications as applied to the aviation environment to better understand its significance for flight safety. Cardiovascular screening guideline recommendations post-infection recovery are suggested based on profile stratification including airperson flight class, tactical military, and aerobatic pilots to provide a suggested approach to inform aeromedical decision making.

METHODS

Literature Review

A qualitative narrative review was performed using the PubMed literature search engine for relevant peer-reviewed articles addressing the implications of mild to severe COVID-19 infection toward heart tissue, circulating cells, and endothelium in high-performance athletes as a correlate for experiencing high G forces, scuba divers as an environmental work analog, occupational and military medicine, and established medical aviation benchmarks toward this target population. Conditions of primary screening concern included hypertension, subclinical myocardial injury as potential proarrhythmic substrate, increased risk of sudden death, myocarditis, pulse and blood pressure lability in response to vigorous activity, cardiovagal and orthostatic dysfunction, and thromboembolic disease. International medical association guidelines, expert consensuses, international societies and government recommendations for athletes, scuba divers, and aircraft pilots were included regarding return-to-work and return-to-play screening guidelines from a cardiovascular perspective via searching the relevant association, organization, or government websites. Given the extensive data pool covering topics overlapping between the cardiovascular system and COVID-19 infection, extracted publication selection was limited to those with greatest perceived relevance to aviation medicine based on the specific topics addressed.

Literature Analysis

A total of 315 sources were retrieved in the English language using the search term groupings [(“covid” OR “sars-cov-2” OR “covid-19”) AND (“heart” OR “cardiac” OR “cardiovascular”)] in combination with boolean operator “AND” plus the following to generate multiple unique searches: (airmen OR pilots OR aircrew OR aeronaut OR aviator), (“players” OR “athletes” OR “professional athletes” OR “sports” OR “athletic”), (“recommendations” OR “return-to-work” OR “return-to-play”), (“scuba” OR “diving” OR “deep-sea” OR “underwater”) in further combination with MeSH terms. Further studies were elicited using citation chasing. An end total of 103 sources meeting relevant criteria for inclusion after detailed review were incorporated.

Classification of COVID-19 Severity, Recovery, and Sequelae

Classification of COVID-19 severity was inconsistent across much of the reviewed literature, with a minority of papers not including infectious stratification. However, certain overlapping criteria did emerge which were used as an approximation. For purposes of this paper, COVID-19 infection is generally classified into four categories based on FAA guidelines:[28] asymptomatic or mild (positive PCR with no symptoms or minimal symptoms treated on an outpatient basis without supplemental oxygen needs), moderate (symptoms requiring hospitalization but not admitted to the intensive care unit), severe (symptoms requiring hospitalization and intensive care unit admission), and prolonged outpatient recovery course. Postinfectious recovery according to the Centers for Disease Control and Prevention is defined as 72 h following defervescence without fever-reducing medications, improvement of respiratory symptoms, and at least 7 d following symptom onset. The duration of persistent or “long-haul COVID-19” symptomology varied, though is generally defined by the literature as lasting from 1 wk to 3 mo or greater, serving as a driving motivator for screening guideline development.

FINDINGS

Retrospective studies of hospitalized patients with confirmed COVID-19 infection determined that both pre-existing cardiovascular risk factors and in-hospital cardiac events carried significantly higher mortality,[51] highlighting a relationship between the heart and COVID-19, though most immediate or long-term complications remain primarily respiratory rather than cardiac.[13] Reported COVID-19 infection associated cardiac complications among all degrees of severity include atrial and ventricular arrhythmia, myocardial infarction, nonspecific cardiomyocyte injury as shown by troponin and CK elevations, atherosclerotic plaque instability, intravascular clot formation, myocarditis,[40] development of heart failure,[27] mild pulmonary hypertension, varying degrees of right ventricular dysfunction,[9] reduced left ventricular function, and chronic heart failure exacerbation.[99] While the precise mechanisms of general cardiovascular complications resulting from viral infection remain under investigation, many theories and preliminary study findings have presented possible physiologic pathways.

Mechanisms of Injury in COVID-19

Mechanisms for such dysfunction are thought to be indirectly due to systemic cytokine storm inflammatory upregulation and directly as a result of COVID-19 transmembrane viral entry into perivascular pericytes and cardiomyocytes.[27,40] This has been demonstrated on autopsy report data, even in expired infected patients without cardiac clinical manifestations.[11] In-vitro studies suggest the virus may also cause fusion of cardiomyocytes.[70] While the viral binding target ACE2 is expressed most highly in the heart and lung, its presence in the vascular endothelium, kidneys, and gut mechanistically allow for myocardial, vascular,[27] and multiorgan dysfunction during severe COVID-19 infection.[40,90,102] Viral endothelial inflammation likely contributes to hypercoagulability and hyperfibrinogenemia[43] with resultant microcirculatory dysfunction leading to observed higher rates of myocardial infarction and thromboembolisms, suggesting theoretical benefit to continuing ACE inhibitor and statin use.[45,47,95] Other potential mechanisms may be secondary to immune-mediation, direct cellular injury, coagulation impairment, and treatment side effects.[43,44,85] Not only may the virus directly affect membrane-specific ion channels predisposing to cardiac arrhythmogenesis,[97] but several common antimicrobials therapeutically used such as hydroxychloroquine, macrolides, and fluoroquinolones have potential to induce lethal ventricular rhythm aberrancies secondary to their known QT prolongation on EKG.[81,96] Use of two or more arrhythmogenic agents in symphony with ICU admission carries the highest complication risk.[64] Aircraft pilots remain a population especially susceptible to these underlying mechanistic complications.

Pilots as an At-Risk Population

Coupled with the systemic inflammation and increased sympathetic outflow of COVID-19 infection, pre-existing cardiovascular disease stands as one of the most significant risk factors for adverse cardiac outcomes.[88] Multiple studies and meta-analyses reviewed cite cardiovascular comorbidities such as coronary artery disease, diabetes mellitus, and most frequently hypertension[56] as being common with infected patients.[23,101] They are linked to an over 10 times higher case fatality rate when compared to control groups.[100] Other mortality risk factors include male sex and advanced age,[62] which describes the predominant proportion of certified pilots in the United States of America according to the 2021 FAA Active Civil Airmen Statistics.[29] Young adult pilots are not excluded, with one Indian report citing a high incidence of hypertension in airpersons at nearly 19%.[9] Overall, pilots with pre-existing cardiovascular disease seem to have higher susceptibility to both viral infection and risk of developing more severe complications,[13,82] including arrhythmias.

Arrhythmias in COVID-19

Abnormal cardiac rhythms during infection should be regarded as a major contributing risk factor for adverse flight outcomes like thromboembolisms and hemodynamic compromise, most concerning in high-G aircraft environments. Atrial fibrillation has been cited as the most common arrhythmia,[40] as well as persistent exertional dyspnea, potentially mediated by reduced myocardial perfusion reserve secondary to coronary microvascular dysfunction such as that in hypertrophic cardiomyopathy.[23] Critically ill hospitalized patients have the highest incidence of not only atrial fibrillation,[41,57] but also myocardial infarction[9] and heart failure.[7,91] The highest rates were seen during severe infection requiring ICU admission[9] and conversely the lowest rates in mild-to-moderate cases.[40,91,92] Deep vein and pulmonary thromboses also occur.[43,44] Elevated serum cardiac biomarkers can be detectable during acute infection,[57] including those without known cardiovascular disease history or prior cardiac arrest, and acute myocardial injury has been attributed in up to 12% of hospitalized patients.[103]

The precise incidences and clinical context of these complications remain elusive. Even in generally older adult hospitalized patients with moderate-to-severe infection, a relatively low number of patients (11.6%) was shown to be diagnosed with acute cardiac complications during admission in a large international retrospective study (most commonly atrial fibrillation in ICU patients) and tended to have multiple pre-existing comorbidities including dyslipidemia, hypertension, chronic obstructive pulmonary disease, and chronic kidney disease.[56] Another large international study among hospitalized majority elderly male adult COVID-19 patients, of whom nearly one-third suffered severe infection, found cardiac complications during admission to be at less than 12%, despite a large prevalence of pre-existing comorbid arrhythmias or coronary artery disease.[56] Resulting vascular pathology from COVID-19 ties into elevated stroke risk as well.[18,47] Interestingly, retrospective data regarding hospitalized patients with influenza virus cite nearly the same incidence of cardiovascular associated events (11.7%), though acute heart failure and ischemic disease were those most correlated with influenza infection.[19] Emerging studies on cardiovascular complications in COVID-19 infection, such as that by Lund,[61] cite much lower postinfection risks compared to those previously done, likely due to earlier data having been obtained from individuals with hospital or ICU admission, often lacking control groups, and potentially subject to selection and surveillance bias. Similar data trend uncertainties have been shown in reports concerning myocarditis as well.

Myocarditis in COVID-19

Controversy has centered on myocarditis, pericarditis, and the unknown implications of associated cardiac screening test abnormalities during follow-up examinations of individuals recovered from acute COVID-19 infection. True incidence of asymptomatic myocardial inflammation lingering after COVID-19 resolution is completely unknown,[35] and reports have been published describing sudden cardiac death even in mild, nonhospitalized COVID-19-positive individuals.[53] One example is a small analysis by Puntmann et al. of 100 individuals from the general civilian population who had recovered from severe COVID-19 infection revealing that almost 80% demonstrated some sign of myocardial inflammation on cardiac magnetic resonance (CMR) imaging up to 3 mo postdiagnosis in conjunction with detectable elevations of high-sensitivity troponin independent from other risk factors.[79] A similar study documented findings of myocarditis, pericarditis, pericardial effusions, and intramyocardial enhancement upon imaging, including in patients without pre-existing comorbidities.[99] Several other case reports cumulatively assessed in a review paper have implicated myocarditis as a prominent secondary manifestation of COVID-19 infection.[25] When patient data among a conglomerate review of cases with only mild infection treated on an outpatient basis were isolated in comparison with healthy cohorts, however, few myocarditis cases were found, suggesting potential data over-interpretation in some previous studies.[61,83,84]

It should be noted that CMR imaging studies did not often include healthy control cohorts and that the significance of myocarditis evident by CMR alone in this clinical context remains uncertain, though related cardiac findings have been associated with mortality risk[38] and should not be overlooked. While the more cost-effective 12-lead EKG can also screen for myocarditis, it is not the gold standard for myocarditis rule-out,[96] must be interpreted in the correct clinical scenario, and CMR holds higher negative predictive value.[80] Such considerations become increasingly relevant for the diagnostic approach to airpersons afflicted with persistent cardiac-related symptoms despite otherwise full recovery following acute infection.

Long Haul COVID-19

The term "long-haul COVID-19" was coined to describe syndromic persistent clinical manifestations for weeks to months following acute infection recovery; this condition has been described in between 40–90% of recovered patients and is most pronounced in survivors of severe infection.[47] Published reports also describe persistent orthostatic intolerance and postural orthostatic tachycardia secondary to autonomic imbalance and heart rate variability on ambulatory electrocardiogram (EKG) recordings up to 3 mo into the post-COVID period.[23,37,101] Comparable findings from Mayo Clinic Hospital were shown using standardized autonomic function metrics, though most diagnosed complications were mild.[86] Other common symptoms with potential cardiac implications following acute recovery are fatigue[35,42,47] and chronic dyspnea,[58,61,71] with infrequent reports of residual myocarditis or pulmonary diffusion impairment.[91]

Recommendations based on a literature review by Mitrani for the general civilian population during the convalescent phase (2–6 mo after COVID-19 infection) include obtaining an initial screening EKG, transthoracic echocardiogram (TTE), cardiac monitor depending on residual symptoms upon routine outpatient followup, and cardiologist referral for all afflicted patients with prior history of myocardial injury during the acute infectious phase (i.e., documentation of elevated troponins, B-type natriuretic peptide, or confirmed ST-elevation myocardial infarction).[66] In limited support for these data, the current aeromedical examiner (AME) coronary heart disease diagnosis protocol for open coronary artery revascularization or left main stenting requires a minimum 6-mo recovery period, 3 mo for stenting excluding left main coronary artery or uncomplicated myocardial infarction, cardiologist referral documentation, Bruce protocol cardiac stress testing (type depending on aeromedical class), postevent cardiac catheterization after 3 to 6 mo, depending on cardiac event recovery time, and possible SPECT myocardial perfusion exercise stress test if indicated based on prior stress test results.[1] These considerations for long-term manifestations potentially secondary to viral infection should also include the rare complicating side effects of the vaccinations meant to prevent them.

Vaccination-Related Cardiovascular Concerns in COVID-19

Risks from vaccination against COVID-19 must be balanced against known complications of infection. For example, common transient side effects such as fever combined with dehydration have been shown to potentially lower G-tolerance in high performance aircrafts shortly following injection, most pronounced following the second vaccine dose.[31] Further unfavorable consequences predisposing to orthostasis cited in an online cohort study included nausea, vomiting, diarrhea, dizziness.[5] Small retrospective studies and scattered case reports also describe associated myocarditis following COVID vaccinations without definitive causal relationship,[23] including young healthy males[55] with one severe case requiring intravenous steroids.[73] A recent pooled analysis encompassing 39 studies with mostly young men receiving vaccination concluded positive association of symptomatic but mild myocarditis after initial dosing with generally complete, rapid resolution and an uncomplicated clinical course.[6] Myocarditis following mRNA-based immunization likely remains an overtly exaggerated and infrequent event with approximate incidence of 1 case per 10,000-100,000 vaccinations, typically self-resolving within several days.[8,30]

A summary of clinical recommendations regarding COVID-19 mRNA vaccination by Luk focuses on supportive care in afflicted patients, appropriate specialist referral, and continued recommendation of vaccination for all approved populations.[60] The Advisory Committee on Immunization Practices (ACIP) and Centers for Disease Control and Prevention (CDC) similarly maintain that the benefits of vaccination far supersede any possible risks.[82] The FAA's most recent position entails a 48-h no fly duty interval observation following each vaccine dose.[28]

Sports Medicine Analog Cardiovascular Concerns in COVID-19

Unrecognized COVID-19 sequelae have potential implications for return-to-work considerations in fitness-reliant occupations. Existing cardiovascular-related literature and return-to-play recommendations for high-performance athletes with prior COVID-19 infection was thus reviewed as a comparable correlate to military and high-performance pilots who undergo physiologically stressful aircraft maneuvers, experience hypoxia, and withstand high G-forces while in flight. While the general array of cardiovascular risks following COVID-19 in athletes are likely analogous to the general population, most investigations have found their rates to be lower overall. A systematic review by Hattum analyzed 12 manuscripts comprising 3131 athletes 18-64 yr of age having received CMR or TTE following COVID-19 infection recovery concluded an overall minimal risk ranging anywhere from 0–5% of associated pericardial or myocardial involvement, arrhythmias, and no reports of sudden cardiac death with reported incidences varying depending on study quality.[94] Another comprehensive prospective study of 90 competitive athletes recovered from asymptomatic or mild COVID-19 with median age of 24 yr screened by bloodwork, 12-lead resting EKG, 24-h ambulatory EKG monitoring, TTE, and cardiopulmonary exercise testing found a low but significant cardiac abnormality in 3.3% of subjects.[16] A similar proposed estimate from literature review of isolated case reports approximates incidence under 3%.[21]

Many studies have separately assessed myocarditis manifested in competitive athletes, specifically known to present less overtly in this target population with nonspecific symptoms such as malaise, reduced athletic performance, or elevated heart rate, while currently standing as the third most common cause for sudden cardiac death in athletes under the age of 35.[35] Outcomes have been variable with inconclusive clinical implications. In one analysis, nearly half of the competitive athletes in the study who recovered from mild COVID-19 had CMR imaging findings suggestive of either possible myocarditis or prior myocardial injury.[80] A similar cohort showed imaging signs of resolving pericardial injury without features, suggesting active myocarditis.[21] In contrast, another elite soccer player cohort followed at 2 mo after mild or asymptomatic COVID-19 had no significantly detectable cardiac biomarker abnormalities.[2] A different professional athletic population screened by obtaining serum troponin, resting and stress-test EKG, and transthoracic echocardiogram (TTE) found no abnormalities.[33] Reported cases have largely been clinically silent and their long-term implications uncertain.

Irrespectively, missed diagnoses of silent arrhythmias, myocarditis, orthostasis, or others can pose detrimental risk to both athletes and pilots alike. Several publications and opinion statements from different medical organizations have attempted to establish cardiovascular screening protocols during and after COVID-19 infection for this target population based on the most up-to-date objective data available. Many expert consensus guidelines highlight the potential gravity of post-COVID-19 cardiac sequelae for asymptomatic or mild infection[14,69,78] in support of return-to-play screening measures. Some independent study recommendations suggested a focused medical history and physical with a 10- to 14-d observation period alone following incidental COVID-19 detection in asymptomatic athletes,[32,35,96] and minimum of chest X-ray, EKG, and TTE if they had confirmed or suspected mild infection prior to gradually resuming competitive sports.[41,77,98] However, a study of 571 competitive junior athletes with mild symptomatic or asymptomatic COVID-19 suggested TTE screening is not recommended given exceedingly low incidence of cardiac involvement,[15] with a separate analysis also supporting no additional cardiovascular screening for mild cases.[35] Another large cohort study of 789 professional athletes fully recovered from asymptomatic or mild COVID-19 (majority 25-yr-old men) found no adverse cardiac events following extensive cardiovascular screening and subsequent sport participation resumption, reinforcing the updated American College of Cardiology expert consensus discouraging cardiovascular risk stratification in athletes fully recovered from mild infection.[63] An additional cohort study produced an analogous verdict,[33] as well as an analysis by Phelan et al. when weighing medical resource utilization and health care costs.[78]

The European Society of Cardiology[84] and Canadian Cardiovascular Society[65] recommendations for moderate and severe COVID-19 infection are the same as those for mild cases in absence of persistent cardiovascular symptoms, echoed by the *Hellenic Journal of Cardiology* recommendations regardless of infection severity.[72] Moderate-to-severe infection in competitive athletes, abnormalities in initial cardiac screening modalities, and any ongoing symptoms such as, but not limited to, chest pain, dyspnea, swelling, palpitations, orthostasis, decreased functional performance, and vital sign aberrations, warrant cardiology referral for continued investigations to likely involve cardiopulmonary exercise testing and CMR imaging.[84,89,98]

Any diagnosis of myocarditis in young, physically active adults requires at least 3 mo of complete rest pending resolution of serum biomarkers of myocardial injury, ventricular systolic function normalization, and specialist clearance in addition to previously mentioned recommendations following exercise testing plus 24-h EKG monitoring per the 2020 European Society of Sports Cardiology, American College of Cardiology, and Dutch Sports Cardiology Section of the Netherlands Society of Cardiology recommendations.[49,76,96] The rationale for temporary discontinuation of competitive play following any classification of COVID-19 infection, especially with myocarditis or pericarditis, is based on the potential for greater cardiac damage due to the virulence-promoting effects during vigorous activity.[10,32] No clear consensus yet exists for clinically relevant cut-offs for troponin levels or imaging findings.

Hyperbaric Medicine Analog Cardiovascular Concerns in COVID-19

Competitive sports and military aviation generally require more stringent athleticism compared to scuba diving, though minimum medical fitness levels are recommended due to the physiologic effects of underwater immersion, including increases in cardiac preload, cardiac output, blood pressure, diuresis, oxygen partial pressure, bradyarrythmogenisis secondary to combination breath holds and hypothermic exposure, and potential secondary effects of decompression sickness, which may all aggravate pre-existing cardiovascular disease.[68] Recreational diving requires at least 6 METs and commercial divers 10 METs with additional reserve of 13 METs in case of underwater emergencies.[54] One expert consensus article addressing return-to-work screening recommendations for fully recovered scuba divers,[54] as well as The European

Underwater and Baromedical Society (EUBS) and the European Committee for Hyperbaric Medicine (ECHM),[26] suggest no cardiovascular-related screening for asymptomatic and mild COVID-19 cases, EKG and TTE for moderate cases, and specialist referral for cardiac stress testing with serum troponin/BNP measurement for severe cases, residual cardiac-related symptoms, or screening test abnormalities. The overall approach to cardiovascular screening guidelines after infectious recovery of scuba divers is relatively more concise, albeit largely comparable to existing aviation authority guidelines.

Published Current Guidelines on COVID-19 from Aviation Authorities

Per the Israeli Aeromedical Center COVID-19 medical screening recommendations,[34] cadet pilots fully recovered from asymptomatic or mild infection constitute a low-risk population and require only a general flight surgeon examination. Moderate and severe cases are to be grounded pending flight surgeon evaluation and specialist consultation once fully recovered. For all fully recovered military and high-performance aviators, a chest X-ray, EKG, and TTE are also required. TTE should additionally be performed for all recovered pilot cadets, regardless of flight class, who have had any documented cardiac manifestations during the disease course. Abnormal screening results necessitate cardiologist consultation and consideration of CMR.

The Canadian Armed Forces Aerospace Medicine Authority recommendations[14] state that grounded aircrew following recovery from mild infection require local clinician assessment for flight clearance, with additional screening chest X-ray and resting EKG for the following indications: cardiac examination abnormalities are found, or aircrew are partially/fully unvaccinated. Moderate COVID-19 illness requires the same workup as mild illness, plus basic laboratory investigations and exertional oxygen testing if indicated per symptomology. If infection was severe, then same as moderate illness plus TTE. Additionally, fighter pilots flying aircraft with ejection seats should either complete a dual flight prior to returning to solo, or positive G_z maneuver warm-up at the start of their first return to solo flying to ensure no respiratory difficulties.[14] Human centrifuge testing has been suggested for medically cleared pilots with recent history of arrhythmia or orthostasis prior to returning to flying high-G aircraft.[52]

As of March 2022, the AME Guide for COVID-19 asymptomatic, mild, and moderate infections allows for medical issuance for complete recovery without residual symptoms. Severe infection history or ongoing cardiovascular symptoms requires FAA deferral with subspecialty follow-up.[28]

Cardiovascular Screening Recommendations for COVID-19 Recovered Pilots

Aircraft type and setting of a pilot's flight profile must be considered by the aeromedical examiner since high-G loading maneuvers are more prone to unmask arrhythmias and overt myoepicardial injury causing hemodynamic compromise or sudden incapacitation in flight. This is further supported by prior animal studies that showed positive G_z loading can histologically lead to cardiomyocyte injury,[12,17] with less clinically pronounced in-vivo studies in human fighter pilots.[20,39,75] The aeromedical history taking should assess for symptoms of palpitations, lightheadedness, presyncope, chest pain, dyspnea, exercise intolerance, calf pain, and worsening fatigue. Cardiac physical exam should pay special attention to jugular venous distention, new murmurs, third heart sounds, popliteal and posterior tibial pulses, extremity edema, and pulse regularity. Resting 12-lead EKGs when performed are ideally compared to prior cardiographic tests since electropathologic changes seen in silent myocarditis can overlap with physiologic changes seen in athletic individuals.[98]

The following aeromedical screening considerations, summarized in **Table I**, are suggested based on comprehensive literature review for pilots seeking medical clearance with a pertinent medical history of fully recovered COVID-19 infection. Asymptomatic civilian pilots seeking Class II or Class III

Table I. Aeromedical Post-COVID-19 Infection Cardiovascular Screening Recommendations for Fully Recovered Pilots Incorporating Existing Literature Review Data, Expert Opinion, and Existing Guidelines for Aircrew Correlates Based on Flight Profile (Civilian Classes I–III, High-Performance Military/Aerobatic), Severity of Viral Illness (Mild, Moderate, Severe), Disease Course Complications, and Ongoing Post-Viral Cardiac-Related Complications.

SEVERITY OF ILLNESS/COMPLICATIONS	RECOMMENDATION
Civilian Recreational and Commercial (Class I-III)	
Asymptomatic/Mild COVID-19	Focused medical history and physical, no further cardiovascular screening in absence of infectious period complications or ongoing symptoms
Moderate/Severe COVID-19	Same for mild, EKG and chest X-ray if Class I, referral if severe infection to cardiology subspecialist for further investigations
Cardiac complications during or after infection/abnormal findings on initial examination or screening tests	Same for moderate/severe, referral to cardiology subspecialist for further investigations
High-Performance, Aerobatic and Military Pilots	
Asymptomatic/Mild COVID-19	Focused medical history and physical, no further cardiovascular screening in absence of infectious-period complications or ongoing symptoms
Moderate COVID-19	Same for mild, plus chest X-ray and EKG
Severe COVID-19	Same for moderate, TTE and serum cardiac biomarkers, referral to cardiology subspecialist for further investigations
Cardiac complications during or after infection/abnormal findings on initial examination or screening tests	Referral to cardiology subspecialist for further investigations, consider human centrifuge testing or dual-flight prior to solo flight in high-G aircraft

medical issuance regardless of COVID-19 severity stratification history, as well as high-performance, aerobatic, military, and Class I pilots with history of asymptomatic/mild infection, all require only a focused medical history and physical without further cardiovascular screening in the absence of infectious period complications or persistently ongoing symptoms. Recommendations for high-performance, aerobatic, and military pilots with history of moderate infection, and Class I pilots with a history of moderate or severe infection carry the same recommendations as previous plus an additional screening EKG and chest X-ray. Severe infection history in high-performance, aerobatic, and military pilots require same as previous plus an additional TTE and serum cardiac biomarkers. Any documented or disclosed cardiac complications during or after infection in all pilot groups, or abnormal findings on initial medical examination and screening tests, requires cardiovascular specialist consultation for further evaluation.

The established increased cardiovascular complication risk in patients having prior comorbid conditions elicits further potential consideration for commercial pilots with documented COVID-19 already holding a relevant CACI (i.e., hypertension, prediabetes mellitus) or a Special Issuance SI (i.e., coronary artery disease, diabetes mellitus, pulmonary hypertension). Consideration may also be given to temporarily restrict the asymptomatic, fully recovered post-COVID-19 pilot while actively undergoing cardiovascular screening to flying with another pilot who did not have COVID-19 or only had mild/asymptomatic infection without subsequent residual cardiovascular complications. This could provide additional in-flight safety by which any sudden incapacitation of the pilot undergoing screening could be managed by another unaffected pilot still able to fly.

Overall, a stepwise approach for AME's should be implemented in stratifying screening based on medical certificate and aircraft type:

1. Assess disease severity and classify based on the following four categories:
   a. Asymptomatic or mild (positive PCR with no symptoms or minimal symptoms treated on an outpatient basis without supplemental oxygen needs).
   b. Moderate (symptoms requiring hospitalization but not admitted to the intensive care unit).
   c. Severe (symptoms requiring hospitalization and intensive care unit admission).
   d. Prolonged outpatient recovery course (i.e., orthostasis, physical fatigue, etc.).
2. Review current pilot health status, medical class certification, aircraft type, and existing medical certification restrictions prior to COVID-19 infection.
3. Proceed with screening recommendations based on Table I. Consider additional medical evaluation or cardiology referral based on clinical judgement of the AME for any pilots holding special issuances, waivers, or CACI, regardless of pilot medical certification class or presence of cardiac symptoms.

In addition to initial cardiac screening protocol, a thorough review of all current medications and special attention to therapies administered during COVID-19 infection, including hydroxychloroquine, ivermectin, macrolides, and fluoroquinolones known for inducing cardiac electrophysiologic alterations should be documented. Recent data support continued use of ACE inhibitors,[3] beta-blockers,[22] angiotensin receptor blockers, and particularly statins for their endothelial-stabilizing and cardiovascular risk-reduction effects during and after COVID-19 illness in patients already on these drugs prior to infection.[59,85,91] No adverse lasting cardiac effects from prior dexamethasone treatment during moderate and severe COVID-19 have been demonstrated[50] and does not separately warrant concern or investigation. Continued cardiovascular physical fitness regimens for grounded pilots already cleared for regular exercise with or without medical supervision can reduce the potential cardiovascular deconditioning following illness recovery and should also be encouraged.[4,10]

DISCUSSION

Addressing the central question of return-to-duty cardiovascular screening following the COVID-19 pandemic involves several considerations such as determining accurate detection of any increased arrhythmogenic risk, which pilots require screening and to what degree, optimal screening test modalities, and occupationally relevant interpretation of screening results. In comparable cohorts such as young athletes, scuba divers, and military personnel, these guidelines have remained variable in approach considering the various clinical challenges of developing an effective strategy. Overall, it is difficult to ascertain the true prevalence of myocardial involvement due to COVID-19 infection in both the general population and airpersons since many investigations study moderate-to-severe disease in hospitalized patients, though some reviews suggest it to be relatively low. Additionally, the infectious course is not predictable, screening tests fall short in sensitivity and specificity, cost-efficacy and worktime losses must be weighed, unnecessary delay for return to duty with negative impacts on already strained operations, and relevant test interpretation requires overlapping expertise in the realm of aviation medical standards. The difficulty in ascertaining causation vs. correlation, plus the skew of more clinically severe infections occurring in elderly patients with multiple coexisting comorbidities vs. healthier patient populations confounds the ability to confidently fit COVID-19 related cardiovascular risk mitigation into the aviation standard "1% rule." Therefore, the use of this review will be highly dependent on the setting and nature of the aeromedical examiner and the evaluated airperson(s).

Cardiac dysfunction during hospitalization and pre-existing cardiovascular comorbidities do seem to prognosticate poorer outcomes, but confounding factors such as outcomes being reported mostly in hospitalized patients of older age with multiple associated risk factors makes it difficult to attribute causality or strong association with COVID-19 viral infection.

While more data are needed to understand the effects of COVID-19 on the human heart, other known viral infections such as influenza and different coronavirus strains do not typically require cardiovascular screenings in the absence of clinical cardiac-related symptoms. It is unclear whether more stringent cardiovascular screening protocols for pilots with pre-existing CACI's or Special Issuance SI's for cardiovascular-related comorbid conditions should be empirically enacted in the absence of clinically manifested cardiovascular symptoms and presence of full infection recovery.

COVID-19-related myocarditis also poses a dilemma for developing screening guidelines due to limited understanding of the significance of cardiac serum marker elevations, physiologic cardiovascular training adaptations confounding EKG and CMR findings, atypical presentation of symptoms by athletic analogs, and insufficient data to predict true prevalence and long-term effects. It is also possible that side effects of COVID-19 infection treatment protocols could have affected some of the milder reported myocarditis cases,[98] as well as other cardiac complications. Ventricular remodeling has also been confirmed to physiologically occur from athletic training and could be confused with myocarditis in fitter cohorts based on volumetric study disparities between COVID-19 positive athletes and healthy controls.[38]

Regarding return-to-play screening guidelines for athletes as a comparable cohort for high performance pilots, the recommendations from the United States of America seem slightly less pragmatic compared to European and Canadian policies,[48] the latter accounting for the growing aforementioned lack of association between COVID illness severity and risk of acquiring myocarditis. More recent appraisal of existing literature suggests a lack of data to confirm association between COVID-19 and myocarditis, leading some authors to argue against return-to-play cardiovascular screening strategies for asymptomatic and mild cases, given no randomized clinical control trials have been conducted to demonstrate utility of aforementioned cardiovascular screening tests.[1] Additionally, despite antecedent viral infection having common association with myocarditis and some other cardiac abnormalities,[53] coronaviruses have historically not been regarded as primarily cardio-trophic viruses[61] and sparse reports prior to the 2019 pandemic largely describe self-limiting cases.[80] To date regarding the current pandemic, some studies support the notion that clinically relevant myocardial injury and dysfunction are self-limiting phenomena confined to the severe illness phase.[61] Diagnosis and treatment for persistent symptoms of long-haul COVID-19 remains under investigation, currently focused on supportive care, reassurance, longitudinal monitoring, and specialist referral where appropriate.

Excessive screening with blood tests, EKG, and cardiac imaging should be avoided as much as possible, since it has a higher likelihood of false-positive findings which may be incidental at best and skews investigational studies.[78] These false positive findings would potentially require further investigation that would then unnecessarily expose individuals to risk in the form of invasive procedures and tests. More research is needed to elucidate the degree to which abnormal cardiac lab and imaging findings observed in post-COVID-19 patients bear clinical significance. Adequate pretest probability of the airpersons tested must be weighed against the limited sensitivity and specificity of existing cardiovascular testing modalities, and a practical approach to medical screening must be balanced against obtaining ideal diagnostic precision. As more COVID-19 surges and strains develop, the associated conditions will continue evolving and influence the future approach to screening airpersons. The basic principles of cardiac screening for other cardiovascular conditions such as hypertrophic cardiomyopathy, channelopathies, and coronary artery disease should not be overlooked when assessing COVID-19 recovered pilots and remains at the foundation of aeromedical cardiovascular examinations.

Several recommendations for screening fully recovered asymptomatic or mild COVID-19 cases in young, healthy populations suggests it may not be necessary, and a targeted approach based on patient symptomology is key. For history of moderate and severe infections, or patients who already experienced new cardiovascular complications while acutely ill, there is not enough evidence to exclude the commonality of patients developing heart problems. Class I pilots and military/high-performance pilots fall into this category where fitness-related sudden cardiac incapacitation poses significant risk to the pilot, passengers, aircraft, and strategic flight objectives. Thus, return-to-work screening is more strongly recommended with a combination of chest X-ray, EKG, TTE, biomarkers, cardiologist referral, and CMR when indicated based on medical history and infection severity. No criteria have yet been definitively established for diagnostic study cut offs for serum markers or imaging in the context of COVID-19 infection, and interpretation remains dependent on holistic evaluation with expert consultation on a case-by-case basis. Future observational cohorts or randomized double-blinded clinical trials may be needed to clarify the true cardiovascular risks of COVID-19 infection, its longitudinal effects, and screening protocol efficacy in reducing flight-associated medical incidents.

The findings and recommendations of this review are relevant for return-to-work cardiovascular screening protocol development for pilots after recovery from COVID-19 infection with the goal of maintaining acceptably low risk for subtle or sudden cardiac incapacitation. Aviation medical examiners should remain cognizant of the clinically apparent and occult manifestations of cardiovascular dysfunction associated with COVID-19 infection when applying return-to-work screening guidelines to ensure high flight safety standards are maintained and sudden incapacitation risk mitigated during the ongoing pandemic. Future research is needed to address gaps in knowledge regarding the cardiovascular implications of novel COVID-19 infection.

Conclusion

In summary, the major COVID-19 cardiopathology associations entail atrial (most common) and ventricular arrhythmias, myocardial infarction, nonspecific cardiomyocyte injury, atherosclerotic plaque instability, intravascular clot formation, myocarditis, heart failure, pulmonary hypertension, biventricular dysfunction, and chronic heart failure exacerbation through several plausible direct or indirect mechanisms. Syndromic persistent clinical manifestations following infection such as orthostasis, fatigue, and autonomic aberrancies which may affect pilot flight performance are common. Relevant clinical outcome data regarding viral infection support the notions that pre-existing cardiovascular disease, cardiac-disease risk factors, and severity of infection increase the likelihood for adverse outcomes of which airpersons remain a susceptible population. The ACIP, CDC, and FAA recommend COVID-19 vaccination for pilots followed by a brief no-fly period to account for the associated minimal risk profile.

High-performance analog population data largely supports existing cardiovascular screening recommendations published by the American College of Cardiology, European Society of Cardiology, Canadian Cardiovascular Society, Hellenic Journal of Cardiology, Dutch Sports Cardiology Section of the Netherlands Society of Cardiology, European Underwater and Baromedical Society, European Committee for Hyperbaric Medicine, and smaller research cohort analyses. These recommendations are reflected in existing aeromedical protocols of the Israeli Aeromedical Center, Canadian Armed Forces, and FAA and are used to present a conservative approach to cardiovascular screening following complete COVID-19 infection resolution according to flight profile. Civilian pilots seeking Class II or Class III medical issuance, as well as high-performance, aerobatic, military, and Class I pilots, with a history of asymptomatic/mild infection all require only a medical history and physical. High-performance, aerobatic, and military pilots with history of moderate infection, and Class I pilots with a history of moderate or severe infection require an additional screening EKG and chest X-ray. Severe infection history in high-performance, aerobatic, and military pilots require an additional TTE and serum cardiac biomarkers with cardiology referral.

Published literature continues to bear significant limitations and future studies should address true prevalence of myocardial involvement due to COVID-19 infection in both the general population and airpersons, further ascertaining causation vs. correlation, addressing confounders in COVID-19 cardiovascular outcome interpretation, and establishing occupationally relevant interpretation of screening results.

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