Diagnostic evaluation and cardiopulmonary exercise test findings in young athletes with persistent symptoms following COVID-19

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ABSTRACT

Objectives Persistent or late-onset cardiopulmonary symptoms following COVID-19 may occur in athletes despite a benign initial course. We examined the yield of cardiac evaluation, including cardiopulmonary exercise testing (CPET), in athletes with cardiopulmonary symptoms after COVID-19, compared CPETs in these athletes and those without COVID-19 and evaluated longitudinal changes in CPET with improvement in symptoms.

Methods This prospective cohort study evaluated young (18–35 years old) athletes referred for cardiopulmonary symptoms that were present>28 days from COVID-19 diagnosis. CPET findings in post-COVID athletes were compared with a matched reference group of healthy athletes without COVID-19. Post-COVID athletes underwent repeat CPET between 3 and 6 months after initial evaluation.

Results Twenty-one consecutive post-COVID athletes with cardiopulmonary symptoms (21.9±3.9 years old, 43% female) were evaluated 3.0±2.1 months after diagnosis. No athlete had active inflammatory heart disease. CPET reproduced presenting symptoms in 86%. Compared with reference athletes (n=42), there was similar peak VO_2 but a higher prevalence of abnormal spirometry (42%) and low breathing reserve (42%). Thirteen athletes (62%) completed longitudinal follow-up (4.8±1.9 months). The majority (69%) had reduction in cardiopulmonary symptoms, accompanied by improvement in peak VO_2 and oxygen pulse, and reduction in resting and peak heart rate (all p<0.05).

Conclusion Despite a high burden of cardiopulmonary symptoms after COVID-19, no athlete had active inflammatory heart disease. CPET was clinically useful to reproduce symptoms with either normal testing or identification of abnormal spirometry as a potential therapeutic target. Improvement in post-COVID symptoms was accompanied by improvements in CPET parameters.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Persistent or late-onset cardiopulmonary symptoms in athletes after COVID-19 may occur despite a benign initial illness and may be associated with elevated risk for inflammatory heart disease. We sought to describe the results of cardiac testing in this specific group, with a focus on the results of cardiopulmonary exercise testing to identify causes for exertional symptoms beyond inflammatory heart disease.

WHAT ARE THE FINDINGS?

⇒ In 21 young athletes undergoing diagnostic evaluation for persistent or late-onset cardiopulmonary symptoms following COVID-19, no athlete was found to have active inflammatory heart disease.

⇒ Cardiopulmonary exercise testing (CPET) successfully reproduced exertional symptoms in almost all (86%) post-COVID athletes but was not associated with significant cardiac abnormalities, providing reassurance for cardiac safety. CPET identified abnormal spirometry in 42%, which was associated with low breathing reserve in some athletes.

⇒ Improvement in cardiopulmonary symptoms in the 13 athletes followed over time was accompanied by improvement in CPET parameters (peak VO_2, oxygen pulse, resting and peak heart rate).

HOW MIGHT IT IMPACT ON CLINICAL PRACTICE IN THE FUTURE?

⇒ In young athletes with persistent or late-onset cardiopulmonary symptoms after COVID-19, CPET was clinically useful. CPET identified either normal testing allowing for clinical reassurance or abnormal spirometry associated with low breathing reserve in some athletes, which represents a potential therapeutic target worthy of further investigation.

INTRODUCTION

COVID-19 caused by the SARS-CoV-2 virus is a multisystem illness that can involve the pulmonary and cardiovascular systems.[1] Young athletes are relatively protected from severe acute sequelae of COVID-19.[2 3] However, prolonged effects of COVID-19, now defined as postacute sequelae of SARS-CoV-2 (PASC), may occur even in those with mild acute illness.[4 5] Current data suggest that the prevalence of PASC may be lower in young competitive athletes (1.2%–14%)[6 7] than in the general population (26%–39%).[5 8] However, due to the large number of COVID-19 cases, the evaluation of ongoing symptoms, particularly those suggestive of cardiopulmonary origin, remains an important issue in post-COVID athletes' clinical care.[9]

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Return-to-play screening in young athletes after COVID-19 has focused on the detection of inflammatory heart disease, such as myocarditis or pericarditis.[10–12] However, a diagnostic evaluation solely focused on inflammatory heart disease may miss sequelae of COVID-19 impacting other systems that cooperate to produce an exercise effort. This is particularly relevant in an athlete presenting with symptoms suggestive of cardiopulmonary origin that newly appear (referred to as 'late onset') or persist after the acute phase of COVID-19 because the likelihood of active inflammatory heart disease causing these symptoms diminishes over time.[12 13] In the absence of inflammatory heart disease, alternate causes of persistent or late-onset cardiopulmonary symptoms in young athletes after COVID-19 have not been well defined.

Cardiopulmonary exercise testing (CPET) allows for integrated assessment of exercise performance and is a tool that can both help calibrate concern for cardiac pathology and assess for abnormalities in other relevant organ systems in patients with cardiopulmonary symptoms. While others have begun to explore the aetiology of cardiopulmonary symptoms after COVID-19 using CPET,[14–23] none have done so in athletes specifically selected for persistent or late-onset symptoms. We therefore undertook the current study with three a priori objectives. First, we sought to assess the diagnostic yield of cardiac evaluation, including CPET, in this specific population of athletes with cardiopulmonary symptoms after COVID-19. Second, to better identify the specific impact of COVID-19, we compared CPET findings in these post-COVID athletes to those in a reference group of healthy athletes who had not had COVID-19. Finally, we evaluated these athletes with persistent or late-onset cardiopulmonary symptoms after COVID-19 longitudinally to describe improvement in symptoms and change in CPET parameters over time.

METHODS

Study setting

The Cardiovascular Performance Program (CPP) at the Massachusetts General Hospital (Boston, Massachusetts, USA) provides clinical cardiovascular care to athletes. From the programme's exercise laboratory opening (1 October 2011) through present, patient data including CPET results were prospectively collected in a research database.[24] Athletes presenting to the CPP for clinical evaluation of cardiopulmonary symptoms after COVID-19 were approached regarding enrolment in a longitudinal CPET study. Data presented for post-COVID athletes are from the baseline clinical evaluation, which occurred between 1 July 2020 and 1 May 2021, and from follow-up research assessment occurring 3–6 months later. Post-COVID athletes were matched (1:2), as detailed in the online supplemental methods, with a reference athlete group without COVID-19 from the research database (online supplemental figure 1).

Study population: post-COVID athletes

Individuals were eligible for study inclusion in the post-COVID group if they were young (aged 18–35) athletes referred for persistent or late-onset cardiopulmonary symptoms after COVID-19 (defined in the online supplemental methods). Persistent symptoms were defined as those present during acute illness (defined as the first 14 days) and continuing >28 days from diagnosis. Late-onset symptoms were defined as those that newly appeared between 14 and 28 days (eg, most commonly on return to exercise) and were still present >28 days from diagnosis. Cardiopulmonary symptoms were defined as exertional intolerance, chest pain, dyspnoea, palpitations, lightheadedness, syncope and cough.

Clinical and research evaluation: post-COVID athletes

All eligible athletes underwent clinical evaluation including history and physical examination. Participants completed a research survey detailing symptoms present during the acute phase (<14 days) that continued or newly appeared at 14–28 days, and that were still present after 28 days from COVID-19 diagnosis. All eligible athletes completed a clinically indicated CPET. Other initial clinical evaluation included 12-lead ECG, high sensitivity troponin (hs-troponin) level and cardiac imaging (transthoracic echocardiography (TTE) and/or cardiac MRI (CMR)) per contemporaneous guidelines.[25 26] ECGs and cardiac imaging were assessed for normality using athlete-specific guidelines.[27 28] To assess the longitudinal trajectory of symptoms and CPET findings, all athletes were invited for follow-up research assessment occurring 3–6 months after initial clinical evaluation, which included survey reassessment of symptoms and repeat CPET.

Cardiopulmonary exercise testing

All CPETs were performed in a single laboratory. Patients underwent an intensity-graded, maximal effort exercise test with continuous gas exchange (Ultima CardiO2; Medgraphics Diagnostics) on the treadmill (Woodway Pro 27, Woodway) or the upright cycle ergometer (Sport Excalibur Bicycle Ergometer, Lode). The exercise protocols and definitions of CPET parameters are detailed in the online supplemental methods.[24]

Statistical analysis

Continuous variables were described using means and SD or medians and IQR and compared between groups (reference athletes, post-COVID athletes at first vs second assessment) using the Student's t-test, Mann-Whitney U test or paired t-test as appropriate. Categorical variables are presented as n (%) and compared by χ^2, McNemar's or Fisher's exact test as appropriate. Analyses and graphical displays were generated using GraphPad (Prism V.7.0d).

RESULTS

Post-COVID athlete characteristics

The cohort consisted of a total of 21 consecutive young athletes (21.9±3.9 years old, 9 female (43%)) who were evaluated for persistent or late-onset cardiopulmonary symptoms after COVID-19. Athletes presented 3.0±2.1 months after diagnosis (range 1.2–8.5 months). The majority (n=16, 76%) presented between January and April 2021, and as such none had been vaccinated for COVID-19 at the time of infection.[29] Baseline characteristics are presented in table 1; no athlete had known cardiac disease.

All athletes were symptomatic during their acute illness, with 1 (5%) having mild, 8 (38%) having moderate illness without cardiopulmonary symptoms and 12 (57%) having at least one acute cardiopulmonary symptom. Initial symptoms and those present >28 days after diagnosis are shown in figure 1A. A total of 14 (67%) athletes developed at least one new late-onset cardiopulmonary symptom that was not present during acute infection but arose between 14 and 28 days after infection, with 48% developing ≥2 late-onset cardiopulmonary symptoms. All athletes reported at least one persistent or late-onset exertional cardiopulmonary symptom (figure 1B).

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Table 1 Demographic information

	Post-COVID athletes (n=21)	Reference athletes (n=42)
Age	21.9±3.9	21.9±3.8
Female sex	9 (43)	18 (43)
Race/ethnicity		
White (non-Hispanic/Latino)	17 (81)	37 (88)
Black	2 (10)	1 (2)
Asian	1 (5)	1 (2)
White (Hispanic/Latino)	1 (5)	3 (7)
Height (cm)	175.2±13.0	174.3±11.6
Weight (kg)	72.8±17.0	73.9±16.7
BMI (kg/m^2)	23.4±2.6	24.1±3.2
Sport type		
Endurance	5 (24)	10 (24)
Team sport	11 (52)	22 (52)
Mixed/other	5 (24)	10 (24)
Level of competition		
Competitive athlete		
High school	1 (5)	2 (5)
Collegiate	14 (67)	28 (67)
Postcollegiate	4 (19)	8 (19)
Recreational athlete	2 (10)	4 (10)
Medical history		
None	9 (43)	20 (48)
Current asthma	3 (14)	6 (14)
Childhood asthma	2 (10)	5 (12)
Anxiety/depression	3 (14)	1 (2)
Attention Deficit Hyperactivity Disorder	3 (14)	8 (20)
Other	6 (29)	9 (21)
Baseline medications		
None	9 (43)	21 (50)
Contraception (pill/device)	6 (29)	5 (12)
Albuterol	3 (14)	5 (12)
Stimulant	2 (10)	7 (17)
Other	7 (32)	10 (24)

BMI, body mass index.

Post-COVID athlete testing results

Symptoms present at the time of clinical evaluation and testing results are shown in online supplemental table 1. Testing included hs-troponin, ECG, cardiac imaging and CPET in all athletes. No athlete had an abnormal TTE or ECG, apart from resting sinus tachycardia in two athletes (10%). TTE was performed in 19 athletes, of whom 11 also underwent CMR due to elevated suspicion for inflammatory heart disease based on the presence/extent of cardiopulmonary symptoms (n=10) or mildly elevated hs-troponin (n=1). Two athletes had a CMR not preceded by TTE. No athlete had imaging evidence of active inflammatory heart disease.[30] Five CMRs (38%) demonstrated isolated late gadolinium enhancement (LGE). LGE was confined to the right ventricular (RV) insertion point or a single segment in four athletes. One athlete had patchy subepicardial and pericardial LGE without elevated inflammatory markers or hs-troponin, pericardial effusion or evidence of pericarditis on examination or ECG.[30] No athlete had evidence of myocardial oedema, which is required in combination myocardial injury (eg, LGE) to establish active myocarditis.

Post-COVID athlete CPET results

CPET results are summarised in table 2. Eighteen athletes (86%) reported the development of their presenting exertional symptom(s) during CPET (online supplemental table 1). Three athletes (14%) had abnormal peak oxygen consumption (pVO_2, <80% predicted) and three (14%) athletes had low-normal pVO_2 (≥80% but <90% predicted). One athlete demonstrated a symptomatic fall in blood pressure immediately (<1 min) after exercise, with reproduction of presenting complaint of lightheadedness. A second athlete had blunted augmentation of systolic blood pressure with reproduction of presenting complaint of dyspnoea. All athletes completed screening spirometry prior to CPET; two athletes' spirometry represented insufficient effort or quality and was excluded from analysis. Of the remaining athletes, spirometry was abnormal in 8/19 (42%), with 6/19 having both abnormal forced expiratory volume in 1 s (FEV_1) and FEV_1/forced vital capacity (FVC), and two athletes having either abnormal FEV_1/FVC (n=1) or FEV_1 (n=1).[31] Most (88%) with abnormal spirometry did not have current or childhood asthma. The exercise ECG did not reveal ischaemic changes or clinically significant arrhythmias in any athlete.

Comparison with reference athlete CPETs

Reference athletes' demographics were similar to post-COVID athletes (table 1). Post-COVID and reference athletes had similar pVO_2 and VO_2 at the ventilatory threshold (table 2). As compared with reference athletes, post-COVID athletes' FEV_1 as a per cent of predicted (86±16 vs 98±12, p<0.01) and FEV_1/FVC (0.74±0.11 vs 0.86±0.06, p<0.001) were lower. Post-COVID athletes had a higher prevalence of abnormally low peak exercise breathing reserve (42% vs 12%, p<0.05) than reference athletes. In post-COVID athletes, low breathing reserve occurred most often in those with both abnormal resting spirometry and normal fitness (pVO_2 80%–120% predicted; 4/8 or 50%) in whom it may represent a true pulmonary limit, rather than in those with normal resting spirometry and supranormal fitness (pVO_2 ≥120% predicted; 3/8 or 38%) in whom it may be physiologic.

Longitudinal post-COVID athlete evaluation

Thirteen athletes (62%) underwent a follow-up research evaluation at 4.8±1.9 months after initial assessment. There were no significant differences in the demographic and CPET parameters in tables 1 and 2 between those athletes who did and did not complete follow-up (all p>0.05). Nine athletes (69%) had resolution of (n=6, 46%) or reduction in (n=3, 23%) cardiopulmonary symptoms at follow-up (figure 2A). Compared with the first post-COVID CPETs, follow-up CPETs demonstrated lower resting heart rate (HR) (81±15 vs 75±10, p<0.05) and peak exercise HR (188±9 vs 183±9, p<0.05) (figure 2C), with no use of medications known to impact HR and similar effort as assessed by the respiratory exchange ratio. pVO_2 increased from 3.39 L/min±0.69 (117±36% predicted) to 3.62 L/min±0.81 (123±38% predicted, p<0.05, figure 2B). The combination of lower peak HR and higher pVO_2 resulted in higher peak oxygen pulse in 11/13 (85%) at follow-up (figure 2D). Similarly, the chronotropic index, which defines the change in exercise HR relative to VO_2 accounting for predicted values, was lower on the follow-up versus the first CPET (0.77±0.20 vs 0.85±0.23, p<0.05, online supplemental table 2). There was numerical improvement in FEV_1 (3.8±1.0 to 4.1±0.9 L, p>0.05) and FEV_1/FVC (0.75±0.12 to 0.79±0.09, p>0.05) that was not statistically significant, and normalisation of abnormal FEV_1

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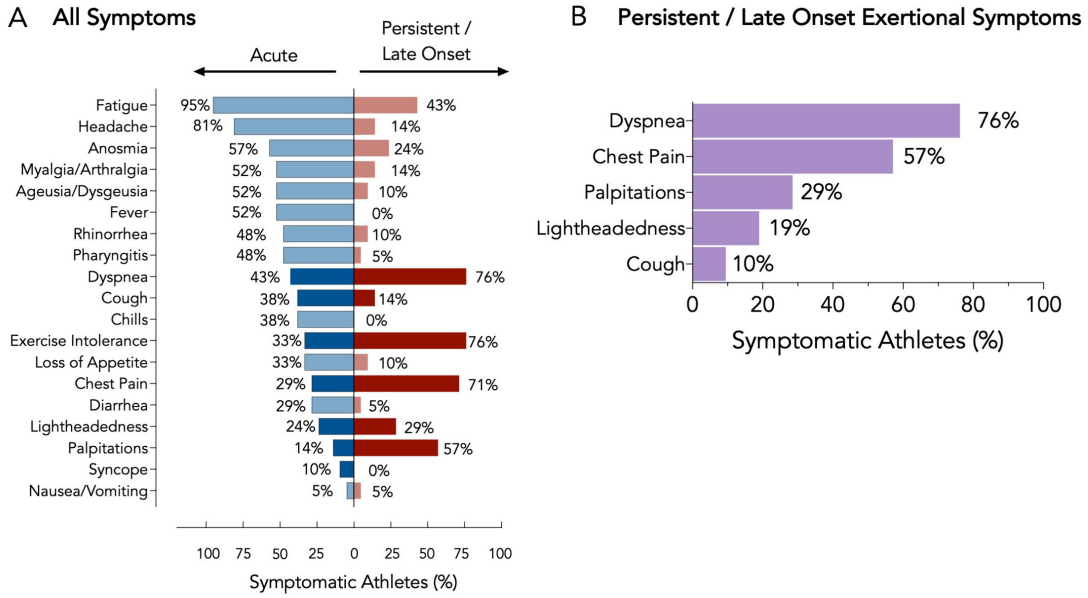

Figure 1 Symptom prevalence. (A) Prevalence of self-reported symptoms during acute COVID-19 (<14 days from diagnosis) and that were persistent (>28 days from diagnosis) or late onset (newly appeared 14–28 days and were still present>28 days from diagnosis) in athletes. (B) Prevalence of self-reported persistent or late-onset cardiopulmonary symptoms that occurred during exertion.

in two of three athletes in whom this was abnormal at baseline (online supplemental table 2). On follow-up evaluation, the exercise ECG did not reveal ischaemic changes or clinically significant arrhythmias in any athlete.

DISCUSSION

This study was conducted to assess the diagnostic yield of cardiac evaluation including CPET and describe follow-up of young athletes with persistent or late-onset cardiopulmonary symptoms following COVID-19. Key findings are summarised as follows. First, while no athlete in this study was asymptomatic during acute illness, the majority of athletes developed at least one new late-onset cardiopulmonary symptom that was not present during acute infection. This highlights the need for ongoing clinical assessment as symptoms may only become evident under the physiological stress of returning to exercise. Second, CPET was clinically valuable in this population as it successfully reproduced athletes' presenting symptoms in the absence of significant cardiac abnormalities, allowing for reassurance. CPET also identified a high prevalence of abnormal spirometry and associated low breathing reserve, which may provide an alternate cause for symptoms and a potential target for treatment. Third, longitudinal evaluation identified small but significant improvements in several CPET parameters that accompanied symptomatic recovery, which may relate to resumption of training or resolution of direct COVID-19 impact. Finally, while the primary focus of return-to-play evaluation has been on the exclusion of inflammatory heart disease, diagnostic evaluation (online supplemental figure 2) revealed no active inflammatory heart disease despite a high cardiopulmonary symptom burden. These results emphasise the importance of consideration for both inflammatory heart disease and other relevant and treatable cardiopulmonary diagnoses in young athletes presenting with persistent or late-onset symptoms after COVID-19.

Clinical utility of CPET in symptomatic post-COVID athletes

Our results demonstrate that CPET is a valuable clinical tool in the population of young athletes with persistent post-COVID symptoms. We previously demonstrated that appropriately customised CPET was effective at reproducing presenting symptoms in athletes without COVID-19, allowing for either the identification of relevant cardiopulmonary diagnoses or reassurance in the presence of normal testing.[32] The current study reaffirms these findings, with almost all athletes reporting their presenting symptoms during the test and most having either normal tests or abnormal resting spirometry. The CPET findings observed, in particular the abnormal resting spirometry coupled in some with low breathing reserve, while not posing risk to return to sport, represent potential opportunities to trial intervention to improve exertional symptoms. Overall, symptom provocation coupled with CPET results in this post-COVID population allowed for provision of reassurance when combined with a comprehensive evaluation, identified potentially treatable abnormalities and facilitated gradual return to play with close clinical follow-up.

Insights into post-COVID symptoms from follow-up evaluation

Our longitudinal data reveal a reassuring reduction in cardiopulmonary symptoms over time in post-COVID athletes. Despite no differences in pVO_2 at baseline between post-COVID and reference athletes, there was improvement in pVO_2 with concomitant improvement in symptoms in post-COVID athletes. These data suggest that deficits in pVO_2 and detraining may have been underappreciated as a cause for symptoms in these athletes' initial evaluation, particularly with the use of prediction equations derived in the general population.[24] While data on physical activity at the two time points were not systematically collected, the improvement in pVO_2 and reduction in resting HR over these athletes' recovery period may represent a retraining effect from return to sport, and underscore the importance of resumption of exercise once an adequately reassuring cardiac evaluation is complete in order to support continued recovery. Conversely, lower peak HR on follow-up CPET is not explained by retraining, and may indicate COVID-19 impact on the autonomic response to exercise as has been suggested by others' work in the general population[33–36] and one prior longitudinal

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Table 2 Cardiopulmonary exercise test data

	Post-COVID athletes (n=21)	Reference athletes (n=42)
Testing modality		
Cycle ergometer	9 (43)	18 (43)
Treadmill	12 (57)	24 (57)
Vital signs		
Baseline HR (beats per minute)	86±16	81±14
Peak HR (beats per minute)	189±9	189±9
Percent predicted	95±4	95±4
Heart rate recovery (beats per minute)	44±12	46±11
Baseline SBP (mm Hg)	122±11	119±11
Peak SBP (mm Hg)	168±21	172±24
Baseline DBP (mm Hg)	75±6	77±8
Peak DBP (mm Hg)	77±5	70±12†
Baseline O_2 saturation (%)	98±1	98±1
O_2 saturation (%) at peak exercise	96±2	96±2
Spirometry*		
Pre-exercise FEV_1 (L)	3.7±1.1	4.1±1.0
Percent predicted (%)	86±16	98±12†
Abnormal (below 5th percentile)	7 (37)	3 (7)†
Pre-exercise FVC (L)	4.9±1.1	4.8±1.1
Percent predicted (%)	98±10	98±13
Pre-exercise FEV_1/FVC	0.74±0.11	0.86±0.06†
Abnormal (below 5th percentile)	7 (37)	1 (2)†
Gas exchange		
Respiratory exchange ratio	1.17±0.09	1.17±0.08
Peak VO_2 (L/min)	3.2±0.7	3.4±0.9
Peak VO_2 (mL/kg/min)	44.6±9.1	46.4±9.6
Percent predicted (%)	110±30	114±23
Abnormal (<80% predicted)	3 (14)	1 (2)
VO_2 at VT (mL/kg/min)	35.7±11.3	36.0±10.3
Chronotropic index	0.89±0.24	0.83±0.17
Oxygen pulse (mL/beat)	16.8±4.2	18.1±4.9
Total VE/ VCO_2 slope	28.1±3.4	28.2±4.0
VE/ VCO_2 slope through VT	24.6±3.3	24.3±3.2
Peak VE (L/min)	112±32	120.±37
Breathing reserve (%)*	18±20	25±19
Low breathing reserve (<10%)	8 (42)	5 (12)†

*Two post-COVID athletes' spirometry measurements (1 male, 1 female) were excluded due to low quality.
†P<0.05 for post-COVID athletes versus reference athletes.
DBP, diastolic blood pressure; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, heart rate; SBP, systolic blood pressure; VCO_2, carbon dioxide production; VE, ventilation; VO_2, oxygen consumption; VT, ventilatory threshold.

study in variably symptomatic athletes.[19] Our results identify important directions for future in-depth work aimed at better delineating the relationships among persistent cardiopulmonary symptoms after COVID-19, detraining and retraining, and these exercise testing parameters.

Comparison to prior published work: CPET and spirometry

Whereas other studies have evaluated post-COVID CPET or spirometry findings either in non-athletes with persistent symptoms or in athletes who were not selected for persistent symptoms,[14–23] to our knowledge, this study is the first to focus on CPET findings in young post-COVID athletes with persistent or late-onset cardiopulmonary symptoms. Despite the presence of prominent symptoms, most athletes in our cohort did not demonstrate significant abnormalities of ventilatory efficiency or pVO_2 on their first CPET, which is consistent with others' results in variably symptomatic athletes.[16 17 20 22] Conversely, we observed a high proportion of post-COVID athletes with mild abnormalities in screening spirometry. Our study is limited in that baseline pre-COVID spirometry was not available and, with a focus on ruling out cardiac disease, full and appropriately customised pulmonary evaluation was not systematically performed. Therefore, we cannot delineate if the higher prevalence of abnormal spirometry in post-COVID as compared with reference athletes was due to COVID-19 or reflects baseline differences between the groups despite careful matching. Others have reported mild decreases in FEV_1 in athlete cohorts that were not selected for persistent symptoms as compared with pre-COVID values[15] or controls,[16] which support the possibility that the observed spirometry abnormalities in our study were due to COVID-19. Given incomplete longitudinal improvement, our study may have been enriched for athletes with mild baseline spirometry abnormalities, and future work should identify if such athletes are at higher risk of developing persistent cardiopulmonary symptoms after COVID-19 or if this represents a limitation of our small cohort size. Overall, our results highlight an important area of future work given the potential for focused pulmonary intervention that may facilitate symptom resolution and return to sport.

Diagnostic approach in symptomatic post-COVID athletes

The diagnostic evaluation of young athletes presenting with persistent or late-onset symptoms following COVID-19 infection remains a clinical challenge. Our results highlight that athletes may develop new late-onset cardiopulmonary symptoms, typically when returning to exercise, despite a benign acute course. While it is appropriate that the presence of these symptoms prompts clinical concern,[37] active inflammatory heart disease after COVID-19 is rare[11 12] and was not present in athletes in this cohort despite a high burden of cardiopulmonary symptoms. Our cohort demonstrated a sizeable prevalence of isolated LGE, which is in line with data from other athlete cohorts without COVID-19 suggesting that LGE, particularly when located at the RV insertion point, is common with unclear clinical significance.[38–40] Limited data suggest that active inflammatory heart disease after COVID-19 resolves within 3 months on follow-up imaging,[12] which further diminishes the likelihood that symptoms may be ascribed to active inflammatory heart disease the later the athlete presents for evaluation after infection.[13] Our diagnostic approach (online supplemental figure 2) integrates symptoms, initial testing, other explanatory diagnoses and time since infection to calibrate suspicion for inflammatory heart disease in athletes presenting with persistent or late-onset cardiopulmonary symptoms, and outlines initial steps, such as CPET, in this patient population that may identify alternate causative diagnoses.

Limitations

There are several limitations to this study in addition to those outlined above. First, athletes were referred to a sports cardiology practice for assessment of cardiopulmonary symptoms and represent a highly select subgroup of post-COVID athletes. Despite this selection, no athlete had active inflammatory heart disease. Importantly, current data[7] support and return-to-play protocols[13 26 41] specify further cardiology evaluation for exactly this type of athlete. Therefore, our work, which assesses the totality of the cardiac evaluation including CPET in this group, provides data in the small proportion of athletes who still require further clinical evaluation prior to return to play after COVID-19. Second, a complete pulmonary evaluation including

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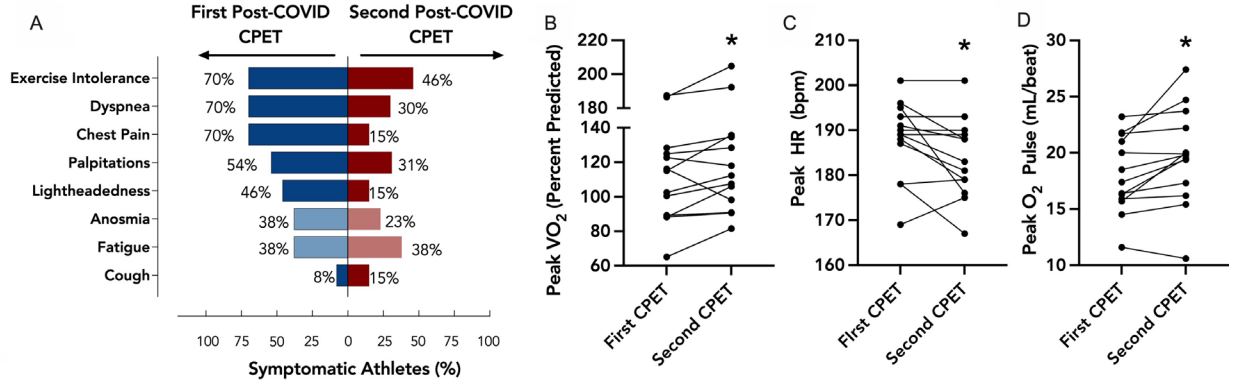

Figure 2 Longitudinal follow-up symptoms and cardiopulmonary exercise testing (CPET) data. (A) Prevalence of self-reported symptoms at the time of the first post-COVID CPET and at the second post-COVID CPET (4.8±1.9 months later). (B) Improvement in pVO_2. (C) Reduction in peak exercise heart rate (HR). (D) Improvement in the oxygen pulse on the second post-COVID CPET as compared with the first post-COVID CPET. *P<0.05 for post-COVID athletes baseline versus follow-up CPET.

full pulmonary function testing and pulmonary imaging was not systematically performed as part of this initial evaluation, whose primary goal was ruling out inflammatory heart disease. We also did not systematically collect downstream data on athletes' non-cardiac medical management. While this limits our ability to define the pulmonary impact of COVID-19, our results provide important preliminary results in an area meriting further study. Third, the absence of baseline diagnostic testing before COVID-19, specifically prior CPET and spirometry, and the incomplete longitudinal follow-up in our cohort limit our ability to conclude whether demonstrated abnormalities were pre-existing, resulted from COVID-19 or were due to associated detraining. However, the use of a well-matched reference group of athletes and longitudinal data on a representative subgroup of post-COVID athletes help highlight the deficits that are most likely to relate to persistent or late-onset cardiopulmonary symptoms in athletes after COVID-19.

CONCLUSION

In a cohort of young athletes presenting with a high burden of persistent or late-onset cardiopulmonary symptoms after COVID-19, no athlete was found to have active inflammatory heart disease. CPET demonstrated clinical utility by provoking presenting symptoms in the setting of largely normal testing results, thus allowing for patient reassurance, and by identifying abnormalities in resting spirometry and breathing reserve that may serve as therapeutic targets. Improvement in cardiopulmonary symptoms over time was accompanied by small but significant improvement in CPET parameters. Further work is needed to better characterise the pulmonary contributions to persistent or late-onset cardiopulmonary symptoms and to define the relative contributions of retraining versus resolution of a direct impact of COVID-19 on post-COVID athletes.

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Contributors NM helped design the study, monitored the data collection, cleaned and analysed the data, and drafted and revised the paper. SKG designed the survey tool, monitored the data collection, cleaned and analysed the data and revised the paper. CS analysed the data and revised the paper. BJP generated the figures and revised the paper. CV monitored the data collection, cleaned the data and revised the paper. TWC revised the draft paper. JSG revised the draft figures and the draft paper. AB helped design the study and revised the draft paper. MMW designed the study, monitored the data collection, cleaned and analysed the data, and drafted and revised the figures and paper. MMV is the guarantor of the study.

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Ethics approval This study involves human participants and was approved by the Massachusetts General Brigham (MGB) Institutional Review Board (study IDs: 2018P00753, 2021P00064), as detailed in the online supplemental methods. Participants gave informed consent to participate in the study before taking part.

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