Panminerva Medica 2024 March;66(1):63-74
DOI: 10.23736/S0031-0808.22.04723-1

SPECIAL ARTICLE

The athlete after COVID-19 infection: what the scientific evidence? What to do? A position statement

Silvia CASTELLETTI [1], Salvatore GERVASI [2], Enrico BALLARDINI [3], Maurizio CASASCO [4], Elena CAVARRETTA [5], Furio COLIVICCHI [6], Maurizio CONTURSI [7], Francesco CUCCARO [2], Flavio D'ASCENZI [8], Giovanni GAZALE [9], Lucio MOS [10], Stefano NISTRI [11], Vincenzo PALMIERI [2], Giampiero PATRIZI [12], Marco SCORCU [13], Andrea SPAMPINATO [14], Monica TIBERI [15], Giovanni B. ZITO [16], Alessandro ZORZI [17], Paolo ZEPPILLI [2] *, Luigi SCIARRA [18] on behalf of Italian Society of Sports Cardiology (SICSport, Società Italiana di Cardiologia), the Associazione Nazionale Cardiologi Extraospedalieri (ANCE), the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO), the Associazioni Regionali Cardiologi Ambulatoriali (ARCA), the Italian Sports Medicine Federation (FMSI, Federazione Medico Sportiva Italiana)

[1]Cardiology Department, IRCCS Istituto Auxologico Italiano, Milan, Italy; [2]Unit of Sports Medicine, IRCCS A. Gemelli University Polyclinic Foundation, Rome, Italy; [3]Sports Medicine Centre, Mantova Salus Group, San Pellegrino Hospital, Mantua, Italy; [4]Italian Sports Medicine Federation (FMSI), Rome, Italy; [5]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University, Latina, Italy; [6]Division of Cardiology, San Filippo Neri Hospital, Rome, Italy; [7]Unit of Sports Cardiology, Centro Polidiagnostico Check-up, Salerno, Italy; [8]Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy; [9]Center of Sports Medicine and Sports Cardiology, ASL 1, Sassari, Italy; [10]San Antonio Hospital, San Daniele del Friuli, Udine, Italy; [11]Cardiology Service-CMSR Veneto Medica, Altavilla Vicentina, Vicenza, Italy; [12]Department of Cardiology, Carpi Hospital, Carpi, Modena, Italy; [13]Department of Sports Medicine and Physical Exercise, ATS Sardegna, Cagliari, Italy; [14]Department of Cardiology, Villa Tiberia Nursing Home, Rome, Italy; [15]Department of Public Health, Azienda Sanitaria Unica Regionale Marche AV 1, Pesaro, Italy; [16]Cardiology Service, ASL Napoli 3 Sud, Pompei, Naples, Italy; [17]Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Padua, Italy; [18]Department of Cardiology, Casilino Polyclinic, Rome, Italy

*Corresponding author: Paolo Zeppilli, Unit of Sports Medicine, IRCCS A. Gemelli University Polyclinic Foundation, Largo Francesco Vito 1, 00168 Rome, Italy. E-mail: paolo.zeppilli@unicatt.it

ABSTRACT

The Coronavirus-19 disease (COVID-19) related pandemic have deeply impacted human health, economy, psychology and sociality. Possible serious cardiac involvement in the infection has been described, raising doubts about complete healing after the disease in many clinical settings. Moreover, there is the suspicion that the vaccines, especially those based on mRNA technology, can induce myopericarditis. Myocarditis or pericarditis related scars can represent the substrate for life-threatening arrhythmias, triggered by physical activity. A crucial point is how to evaluate an athlete after a COVID-19 infection ensuring a safe return to play without increasing the number of unnecessary disqualifications from sports competitions. The lack of conclusive scientific data significantly increases the difficulty to propose recommendations and guidelines on this topic. At the same time, the psychological and physical negative consequences of unnecessary sports restriction must be taken into account. The present document aims to provide an updated brief review of the current knowledge about the COVID-19 cardiac involvement and how to recognize it and to offer a roadmap for the management of the athletes after a COVID-19 infections, including subsequent impact on exercise recommendations. Our document exclusively refers to cardiovascular implications of the disease, but pulmonary consequences are also considered.

(*Cite this article as*: Castelletti S, Gervasi S, Ballardini E, Casasco M, Cavarretta E, Colivicchi F, *et al.*; SICSport, ANCE, ANMCO, ARCA, FMSI. The athlete after COVID-19 infection: what the scientific evidence? What to do? A position statement. Panminerva Med 2024;66:63-74. DOI: 10.23736/S0031-0808.22.04723-1)

KEY WORDS: SARS-CoV-2; COVID-19; Athletes; Myocarditis; Vaccines; Return to sport.

The Coronavirus-19 disease (COVID-19) related pandemic have deeply impacted human health, economy, psychology and sociality. Unprecedented challenges to medical communities arose, requiring quick and efficient answers from health systems.[1, 2] Besides the common respiratory injuries, possible serious cardiovascular sequelae[3-6] of the infection have been increasingly described, raising doubts about complete healing after the disease in many clinical settings. The clinical relevance of cardiac involvement in COVID-19 disease is the heart of a debate and the topic is still under scientific evaluation.

Moreover, although the advent of vaccines represents the main hope of ending the pandemic, there is the suspicion that, especially those based on mRNA technology, can induce rare cardiac adverse effects including vaccine-related myopericarditis.[7]

On the other hand, people would like to perform recreational sports and competitive/professional athletes to resume their activity, asking the medical community to determine when is safe and appropriate to allow their return to play.[8-10] The lack of conclusive scientific data significantly increases the difficulty to propose recommendations and guidelines on this topic. At the same time, the psychological and physical negative consequences of unnecessary sports restriction must be taken into account.

A crucial point is how to evaluate an athlete to this goal. Which is the best diagnostic flowchart and in which individuals? Is it possible to personalise indications, taking into account the different sports and the different clinical manifestations of the disease? What about the asymptomatic subjects who tested positive for COVID-19? Are the return-to-play protocols based on ECG, troponin and echocardiography enough? And finally, given the growing number of vaccinated athletes, how to suspect, identify and manage possible side effects of the vaccination on the heart?

The present document aimed to answer those questions. We first provide an updated brief review of the current knowledge about the COVID-19 cardiac involvement and how to recognize it. In the second part of the document, we present some emblematic cases and reasonable management of an athlete after a COVID-19 infection. It is important to underline that these suggestions are based on experts' opinion and are not supported by strong scientific evidence. Our document exclusively refers to cardiovascular implications of the disease, but pulmonary consequences are also considered (Figure 1).

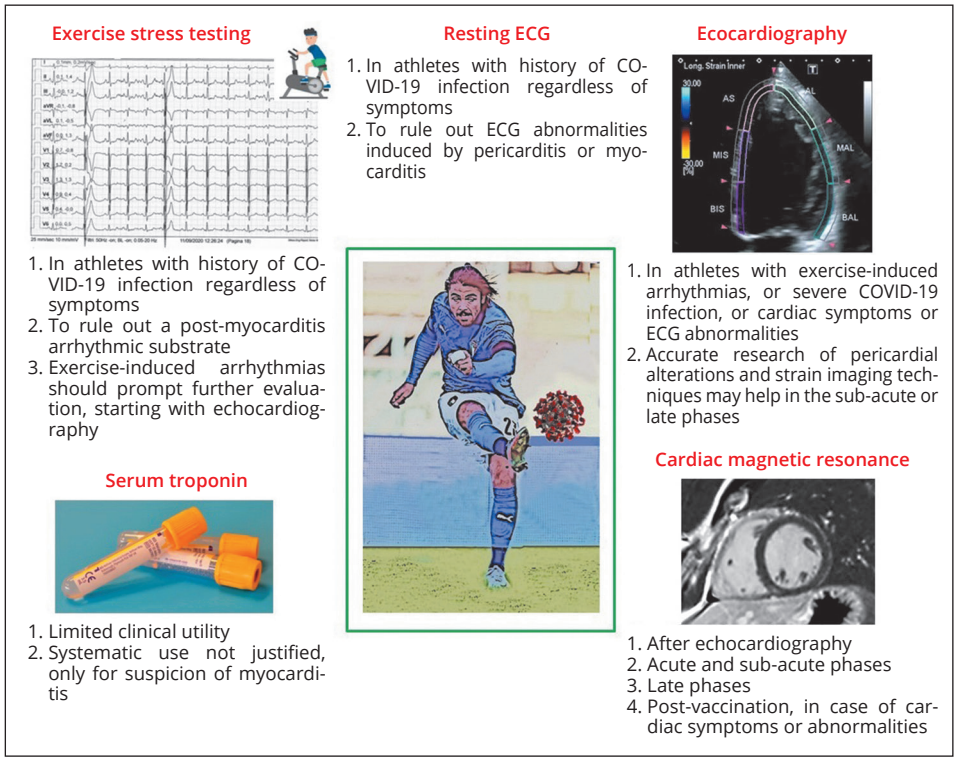

Figure 1.—Graphical abstract.

Background

COVID-19 cardiac involvement: focus on the athlete

Viral myocarditis has an incidence rate of 10-22 per 100,000 individuals and despite the fact that it can affect people of all ages, ethnicities and genders, it is more prevalent in early and middle adulthood.[11] It is a rare but well-recognized cause of sudden cardiac death, with a pooled estimate of 6.1% [4.5-8.2] in athletes *versus* 8.9% [4.9-15.5] in non-athletes, based on a recent systematic review and meta-analyis.[12] Since the initial worldwide spreading of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), much concern has raised due to its possible tropism for cardiomyocytes. In fact, the COVID-19 presents a wide range of clinical manifestations, which includes flu-like symptoms, as cough, fever, fatigue and shortness of breath but also, in the severe forms of the disease, acute respiratory distress syndrome and multiorgan failure.

The cardiac involvement with acute myocardial injury has been frequently reported in 10 to 35% of severe and critically ill patients, but the exact incidence rate of COVID-19-related myocarditis is still unknown.[13]

Multicenter autopsy studies have reported a low incidence (7.2%) of acute myocarditis, as defined by the Dallas criteria, while myocardial injury, *i.e.* perivascular and myocardial inflammatory infiltrate, endocardial and small vessel thrombosis, endothelins and myocyte degeneration, were commonly observed.[14, 15] The cardiac tropism of the COVID-19 has been proved by the detection in endomyocardial biopsy specimens of virus-like particles and RNA by Real-Time PCR and electron microscopy.[16] The host cell receptor for the SARS-CoV-2 is the biologically angiotensin I converting enzyme 2 (ACE2) receptor, expressed in the nasal and pulmonary epithelial cells, in the human ventricular myocardium and in other tissues. In particular, recent studies have demonstrated the ACE2 expression in cardiac myocytes and pericytes, which supports the microvasculature throughout the myocardium, but not in endothelial cells.[17, 18] The ACE2 expression and direct cardiomyocytes and pericytes susceptibility to COVID-19 infection has been proved in cellular models, where the infection produced direct cytotoxic effects and activated the innate immune response, including interferon signalling, apoptosis and reactive oxidative stress.[19, 20] While ACE2 expression is upregulated in cardiomyocytes of heart failure patients,[18] regular physical exercise is protective by inducing a shift in the renin-angiotensin system balance, downregulating the systemic and tissue ACE/Ang II/ATR1 axis, thus upregulating the ACE2/Ang$^{1-7}$/Mas axis, which exerts a benefic effect against cardiometabolic diseases.[21] In addition to the direct cardiovascular injury due to COVID-19 infection, indirect damages related to hypoxemia, microvascular injury and thrombosis, hyper inflammation and pro-inflammatory cytokine storm, abnormal immune dysfunction and platelets hyperactivation, associated with autonomic dysfunction, may cause cardiac injury.[22]

Susceptibility to COVID-19 infection is not different between athletes and non-athletes, as demonstrated by the high incidence of disease in young people and athletes,[23] but their clinical course is generally asymptomatic or mildly symptomatic. In the different studies conducted in the athletic population, the prevalence of asymptomatic individuals ranged from 17 to 54%,[9, 24, 25] with most of the athletes being mildly symptomatic for flu-like symptoms, fatigue, short-lasting fever and ageusia (29 to 83%),[25, 26] at the same time the severe form of the disease requiring hospitalization was exceptional (Table I).[9, 24-36] In the population of junior athletes, the prevalence of asymptomatic individuals is higher, with the incidence of cardiac complications being lower as compared to the population of adult athletes.[36]

Based on the current criteria, the prevalence of clinically diagnosed myocarditis was low, ranging from 0 to 3%[24, 25, 27, 29, 31, 32] only in one study.[28] In a study conducted in a small cohort of professional soccer players,[36] no cases of myocardial involvement were found. However, it was performed during the "first wave" of the pandemic, caused by the original form of the virus. In the two largest and multicenter US studies, the prevalence of clinically proven myocarditis was also very low: 0.5% in the Big Ten COVID-19 Cardiac Registry[30] and 0.6% in the Outcomes Registry for Cardiac Conditions in Athletes.[26] On the contrary, cardiac magnetic resonance (CMR) findings have demonstrated a higher prevalence of signs of myocardial injury and myocarditis, even in asymptomatic/mildly symptomatic athletes, with normal ECGs, echocardiographic studies and normal levels of troponin. At the beginning of the experience, a single-centre cohort study by Rajpal *et al.*[24] reported a dramatic prevalence of myocarditis diagnosed with CMR criteria in 15% (4 out of 26 competitive athletes), without clinically diagnosed myocarditis, which raised much concern for the return to play. In the US multicentre CMR studies, the presence of myocarditis was less common, ranging from 0.5%[26] to 2.3%.[30] However, larger studies reported a much lower prevalence of CMR findings consistent with myocarditis in athletes after COVID-19 infection (see below) and very recently Szabo *et*

TABLE I.—*Studies on athletes with COVID-19 infection.*

Study	N. total	N. COVID+	Athletes	Female N. (%)	Age, mean (range)	Asymp	Mild	Moderate (>7 days)	Severe
Gervasi[27]	30	18	Professional soccer	0 (0%)	22 (21-27)	6 (33%)	12 (67%)	0 (0%)	0 (0%)
Rajpal[24]	26	26	Competitive, mixed sports	11 (42%)	19.5	14 (54%)	12 (46%)	0 (0%)	0 (0%)
Clark[28]	111	59	Collegiate, mixed sports	37 (63%)	20 (19-21)	13 (22%)	46 (78%)	0 (0%)	0 (0%)
Vago[25]	42	12	Elite, mixed sports	10 (83%)	23 (20-23)	2 (17%)	10 (83%)	0 (0%)	0 (0%)
Malek[29]	26	26	Consecutive elite athletes, mixed sports	21 (81%)	24 (21-27)	6 (23%)	14 (54%)	5 (19%)	1 (4%)
Daniels[30]	2461	1597	Collegiate athletes, mixed sports	633 (39.6%)	NA	NA			
Starekova[9]	145	145	Collegiate athletes, mixed sports	37 (25.5%)	20 (17-23)	24 (17%)	71 (49%)	40 (27.6%)	0 (0%)
Brito[31]	54	54	College students athletes, mixed sports	9 (15%)	19 (19-21)	16 (30%)	36 (66%)	2 (4%)	0 (0%)
Hendrickson[32]	137	137	Collegiate athletes	44 (32%)	20 (18-27)	25 (18%)	75 (76%)	37 (33%)	0 (0%)
Moulson[26]	3018	2820	Collegiate athletes	957 (32%)	20	887 (33%)	789 (29%)	663 (25%)	5 (0.2%)
Martinez[33]	789		Professional athletes	12 (1.5%)	25 (19-41)	329 (42%)	NA	NA	0 (0%)
Cavigli[34]	90	90	Competitive athletes	26 (29%)	24 (10)	21 (23%)	69 (77%)	0 (0%)	0 (0%)
Szabó[35]	147	147		53 (36%)	23 (20-28)	19 (13%)	80 (54%)	43 (29%)	5 (3%)
Cavigli[36]	571	571	Non-professional competitive athletes	221 (39%)	14.3	284 (50%)	287 (50%)	-	-

al. have shown a modest frequency of myocarditis among athletes following a COVID-19 infection, being this frequency similar to healthy sex-matched and age-matched athletes without a history of COVID-19 infection.[35]

Moreover, most CMR abnormalities consisted of segmental late gadolinium enhancement (LGE) and myocardial edema, which may be related to acute myocardial injury but are also dynamic: long-term follow-up data are needed to assess their natural history and clinical significance.

Role of cardiac imaging for identification of COVID-19 related acute myocarditis or post-myocarditis scars

Although early cardiac imaging studies have demonstrated cardiac involvement in a significant number of patients and athletes who had recovered from COVID-19 infection,[38] the same results have not been reproduced in more comprehensive studies including larger populations.[9, 26, 31]

Brito *et al.* studied 54 college athletes at a median time of 24 days after asymptomatic (16, 30%) or mild-moderate (38, 70%) infections that did not require hospitalization. Of note, 25% of the symptomatic athletes reported cardiac symptoms. Imaging abnormalities were detected in 27 athletes, the most prevalent being pericardial involvement (13, 48%). It is worth noting that neither myocardial inflammation nor myocardial scar was present in any patient and the most common echocardiographic abnormality detected consisted of reduced global longitudinal strain, whilst only a patient had impaired left ventricle function. A low prevalence of cardiac involvement has also been confirmed in larger studies. In a cohort of 145 competitive athletes, mostly recovered after a mild (49%) or moderate (27.6%) COVID-19 infection, myocarditis was detected only in two athletes by CMR, of note only one had myocardial scar.[9] A large study including 19,378 young competitive athletes who recovered from mainly asymptomatic (33%) or paucisymptomatic (29%) COVID-19 infection, 0.09% had echocardiographic abnormalities and 21 athletes had CMR abnormalities, including isolated pericardial effusion. During a follow-up of 113 days, only one adverse event was observed, likely unrelated to the infection.[26] A recent multicenter study conducted in 571 junior athletes (14.3±2.5 years) demonstrated a low prevalence of cardiac involvement after SARS-CoV-2 infection, with a final diagnosis of pericarditis found in 0.4% of the population and no cases of myocarditis.[36] It is worth noting that the definition of "myocardial injury" differs among the studies: in some studies, the presence of scar without myocardial edema has been considered a sign of COVID-19 related myocardial injury, even though an isolated scar could be due to an old event not related to the COVID-19 infection.

All these data seem to reconsider the frequency of cardiac involvement in asymptomatic or mildly symptomatic young athletes after COVID-19 infection and the use of systematic imaging screening in athletes before the return to play.

Therefore, cardiovascular screening of athletes after COVID-19 should primarily aim to detect acute viral

myocarditis or post-myocarditis scars that may be the source of ventricular arrhythmias.[39] In most return-to-play protocols, transthoracic echocardiography has been suggested as first-line imaging technique to exclude a cardiac involvement considering that cardiac biomarkers rise and ECG abnormalities may quickly resolve.[40-42] Echocardiography may support the diagnosis of acute myocarditis,[43, 44] as it permits a safe and low-cost evaluation of regional and global function[45] and, for this reason, it plays a key role in the care of COVID-19 inpatients.[46-50] Strain imaging techniques may help to detect cardiac involvement in the sub-acute or late phases after a COVID-19 infection, however they are time-consuming and need specific great expertise. Moreover, post-myocarditis myocardial scars are typically segmental and involve the subepicardial/mid myocardial left ventricular layers that contribute less to myocardial thickening. For this reason, they may often be undetectable by echocardiography.[51] Furthermore, echocardiography carries the great limitation of being unable to perform a proper tissue characterization, which plays a key role in detecting cardiac involvement in the sub-acute or post-myocarditis phase. In the peculiar setting of athletes evaluation, it may be difficult to distinguish between physiological remodelling of the athlete's heart and pathological patterns[19] and the routine echocardiographic assessment of athletes after a COVID-19 infection may raise unjustified concerns due to incidental findings. The number of false-negative may be reduced only if the exam is performed by experienced cardiologists who are able to notice even subtle changes (mainly thank to the strain imaging techniques) and/or pericardial alterations (minimal effusion, enhanced pericardial signal, etc.). A previous echocardiogram for comparison may be useful in the diagnosis.[52]

Cardiac magnetic resonance (CMR) is considered the gold standard for the identification of myocardial abnormalities related to myocarditis.[53] However, CMR is not available worldwide and has relevant costs: as such, it cannot be proposed as a first-line screening modality. Accordingly, it is essential to identify the clinical parameters that may prompt further investigations, including echocardiography and CMR. In this context, the clinical history of the infection by COVID-19 (the more severe the symptoms, the highest the likelihood to detect cardiac complications), the presence of cardiac symptoms and the demonstration of ECG abnormalities and ventricular arrhythmias (particularly when induced by exercise) may represent relevant red flags that should prompt imaging evaluation with both echocardiography and CMR.[34]

Role of serum troponin and exercise testing for the identification of COVID-19 related acute myocarditis or post-myocarditis scars

Serum troponin

Myocardial injury, defined as an elevation in cardiac troponin, occurs in a sizeable proportion of patients with COVID-19 and is a well-identified prognostic marker, being associated with progressive heart failure, arrhythmia and death. Multiple mechanisms can explain troponin elevation during COVID-19, including ischemia (caused by either microvascular disease or hypoxia) and direct myocardial inflammatory damage.[54]

Most return-to-play protocols have included troponin sample[40] with the aim to detect ongoing myocardial inflammation. However, the sensitivity and specificity of elevated serum troponin for COVID-19-related acute myocarditis in athletes remain to be established and several considerations may limit the clinical utility of the test in this setting. First, the majority of young healthy athletes develop no or mild symptoms following COVID-19 infection, while a myocardial injury is more often detected in patients with severe COVID-19. Second, it is well known that mild troponin rise is not uncommon after prolonged strenuous exercise, as a consequence, it is recommended to observe a resting period of at least 48 hours before the troponin sample. Third, there is a lack of established troponin reference ranges for athletes. Finally, a troponin value within the range of normality does not rule out both myocardial inflammation and, most importantly, a healed myocardial injury (post-myocarditis myocardial scar) that can be the substrate of life-threatening ventricular arrhythmias.[55]

Table II[9, 24, 26, 28, 30, 31, 33] summarizes the results of the main CMR studies that assessed the prevalence of myocardial/pericardial abnormalities in athletes who suffered COVID-19 infection and the correlation between troponin results and CMR findings.[9, 24, 26, 28, 30, 31, 33] Overall, these studies showed that troponin above normal values can be found in ≈1% of athletes after COVID-19 infection (asymptomatic or with mild symptoms in most cases) and that the correlation with CMR findings is moderate-to-poor.

Mascia *et al.* specifically addressed the clinical utility of the troponin test in a sample of 58 élite soccer players, 13 of whom suffered from COVID-19 infection.[56] They found increased troponin values in 2/13 (15%) athletes with and 2/45 (5%) athletes without COVID-19 infection (P=0.21). All four athletes with troponin elevation underwent CMR that excluded any cardiac injury.

TABLE II.—*Correlation between serum troponin test and cardiac magnetic resonance findings in athletes after COVID-19 infection.*

Reference	Athletes with CMR	Troponin elevation	CMR abnormalities	Correlation troponin-CMR
Rajpal *et al.*[24]	26	0 (0%)	4 (15%) myocarditis 8 (30%) LGE w/o inflammation	Poor
Brito *et al.*[31]	48	1 (2%)	19 (40%) pericardial LGE 1 (2%) myocardial LGE 7 (5%) reduced LV EF and/or GLS	Poor (unknown CMR results in the only athlete with elevated troponin)
Clark *et al.*[28]	59	?	1 (2%) myocarditis 1 (2%) pericarditis	Poor (both athletes with positive CMR had normal troponin)
Starekova *et al.*[9]	145	?	2 (1.4%) myocarditis	Moderate (1/2 athlete showed positive troponin with a "rise and fall" pattern)
Martinez *et al.*[33]	27 of 789	6/789 (0.7%)	3/27 (11%) myocarditis 2/27 (7%) pericarditis	Moderate (2/5 patients with positive CMR had troponin elevation)
Moulson *et al.*[26]	317 of 2820	24/2719 (0.9%)	21/317 (7%) CMR abnormalities	Poor (2/21 patients with positive CMR had troponin elevation)
Daniels *et al.*[30]	1598	?	2 clinical myocarditis Subclinical probable myocarditis Possible subclinical myocarditis	Poor (6/37 patients with positive CMR had troponin elevation)

In summary, given the available evidence, systematic use of troponin samples for screening athletes who suffered from COVID-19 does not seem justified. The test should be reserved for selected cases, in particular when symptoms or abnormalities on other cardiac investigations suggest the possibility of ongoing myopericarditis.

Exercise testing

The healing process of myocarditis may cause myocardial scarring that may be the substrate for re-entrant ventricular tachycardia and sudden death.[57, 58] There is increasing evidence that premature ventricular beats (PVBs) at exercise testing, particularly those with a right bundle-branch-block morphology and a wide QRS (suggesting an origin from the left ventricle) and that increase in number and complexity with increasing exercise load, may predict an underlying myocardial scar also in athletes with normal resting ECG and echocardiography.[59-61] For this reason, exercise testing for the detection of exercise-induced ventricular arrhythmias appears a promising test for ruling out a post-myocarditis arrhythmic substrate in athletes who suffered COVID-19 infection.

Cavigli *et al.* screened 90 athletes with previous COVID-19 infection with blood testing, ECG, ambulatory ECG monitoring including a training session, echocardiography and cardiopulmonary exercise testing. Only one athlete showed relevant uncommon ventricular arrhythmias (isolated PVBs and couplets) at exercise testing: this patient underwent CMR suggestive of acute myocarditis.[34] In another study, 2/24 post-COVID athletes showed PVBs at cardiopulmonary exercise testing: however, in both cases the arrhythmias had been already described in previous tests and CMR was negative.[62]

These preliminary findings suggest the potential utility of new-onset ventricular arrhythmias with uncommon morphology at exercise testing for raising the suspicion of postinflammatory myocardial damage. However, exercise-testing findings were not available for most athletes included in main post-COVID CMR studies[9, 24, 26, 28, 30, 31, 33] and the correlation between exercise-induced ventricular arrhythmias and CMR findings in this particular setting remains to be evaluated.

Vaccines and vaccine-related myopericarditis

Despite the largely demonstrated safety and efficacy of the vast majority of anti-COVID-19 vaccines,[63] they can bring rare side effects. Beyond the life-threatening adverse events related to vaccine-induced immune thrombotic thrombocytopenia and anaphylaxis, vaccines can trigger acute myopericarditis.[64, 65] For this reason, evaluation of athletes after vaccination and after COVID-19 infection raises similar concerns. Usually, myopericardits is observed in young individuals who received mRNA vaccines, with the first manifestations a few days after the second dose, but some cases have also been reported after the first dose.[55, 64] The reported incidence in the biggest registries is around 4.8-12.6 cases per million doses among individuals 12 to 39 years of age, with male predominance.[66, 67]

The underlying mechanisms are unclear. Molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens, immune response to mRNA, anomalous activation of immunologic pathways and dysregulated cytokine expression have been proposed.[68]

Clinical manifestations may include chest pain/discomfort, increased troponin and/or C-reactive protein levels, ECG abnormalities (ST elevation), CMR findings suggestive of myopericarditis.[69]

The clinical course seems benign in the vast majority of cases, with the resolution of symptoms and of most of the abnormalities in a few days, often not requiring hospitalisation. It remains to be clarified whether these myopericarditis secondary to vaccines could cause the formation of potentially arrhythmogenic scars. At the moment, no vaccine-related major cardiac events have been reported in this population in literature. In any case, in our opinion, an athlete suffering myopericarditis after vaccination should be managed in the same way as viral myopericarditis.[45, 70]

Clinical scenarios

Athletes hospitalized for COVID-19 infection

We report the clinical history of a football player who suffered from COVID-19 viral infection which resulted in a significant myocardial involvement. This fearsome complication of COVID-19, even if not very frequent, must always be investigated and excluded before re-admitting an athlete to his previous sport activity.

Case 1: an amateur football player

A 42-year-old amateur football player was recovered in the Emergency Department after three days of cough, fever, dyspnoea, asthenia and myalgia. Familial, personal and medical history were unremarkable. The preparticipation cardiovascular evaluation performed yearly had been negative and, in the past, no further evaluations were required. At first evaluation, he had fever (38.5 °C) and tachypnoea. The oxygen peripheral saturation was 94% (SO_2) which decreased to 91% following a small exercise (walking). He underwent further examination with ECG which was unremarkable, chest x-ray demonstrating increased reticular pattern, ground-glass opacities and bilateral images of consolidation, and blood analysis showing leukopenia, elevated CRP to 1.7 mg/dL (normal value <1 mg/dL) and D-dimer to 858 ng/dL (normal value <500 ng/dL). His blood gas sample showed a P/F value of 240, and his PCR nasal-pharyngeal swab tested positive for COVID-19. For these reasons, he was admitted to a specific COVID-19 ward where he was initially treated with heparin, steroids and respiratory support with oxygen. During the first days of hospitalization, we observed a progressive worsening of the patient's respiratory data and, subsequently, of his clinical status with the appearance of frequent PVBs (right bundle branch block morphology, wide QRS and superior axis) on 12-lead resting ECG. Non-invasive ventilation was started and remdesivir was added to his therapy. At this point, marked elevation in troponin I and slightly reduced systolic left ventricular function (50%) on echo were observed. In the following days, the athlete improved. On day 12 of his hospital stay, the patient underwent CMR which showed small pericardial effusion, a slight reduction of ventricular function (EF=45%), edema pattern of antero-lateral mid-apical wall and sub-epicardial focal late gadolinium enhancement (LGE) in the same segments: all these findings support the diagnosis of acute myopericarditis. Although after 20 days the athlete was well enough to be discharged, he was not considered eligible to restart competitive sport activity: we have recommended only mild leisure activity. We will test this athlete again with echo, cardio-pulmonary exercise test, ambulatory ECG monitoring including a training session, functional pulmonary tests and a second CMR 3-6 months after discharge. In case we obtain favourable results, we will consider re-admitting our athlete to competitive football practice.

Athletes with a history of mild or asymptomatic COVID-19 infection

Case 1: a professional soccer player with new-onset ventricular arrhythmias

This case refers to a 27-year-old professional soccer player. He never had abnormalities at periodic preparticipation screening that includes resting ECG every six months, exercise testing every year and echo every two years. He tested positive for COVID-19 infection at a PCR nasal-pharyngeal swab performed during the routine screening of professional teams. His positivity lasted for ten days, during which he manifested only dysgeusia and dysosmia for three days. After testing negative, he underwent the "return-to-play" protocol as provided by the Italian law.[10] Blood samples were normal, including hsTroponin I. The resting ECG was also normal, while the exercise stress test showed frequent, isolated, monomorphic PVBs (Figure 2A). The 24-hour ECG ambulatory monitoring, including a training session, showed frequent, isolated, monomorphic PVBs (2629/24 hours, right and left bundle branch block), largely predominant during physical activity. Trans-thoracic echo was substantially normal with the exception of an enhanced pericardial signal of the left posterior wall. The CMR showed "very thin subepicardial LGE in the mid-basal inferior wall and very thin intra-

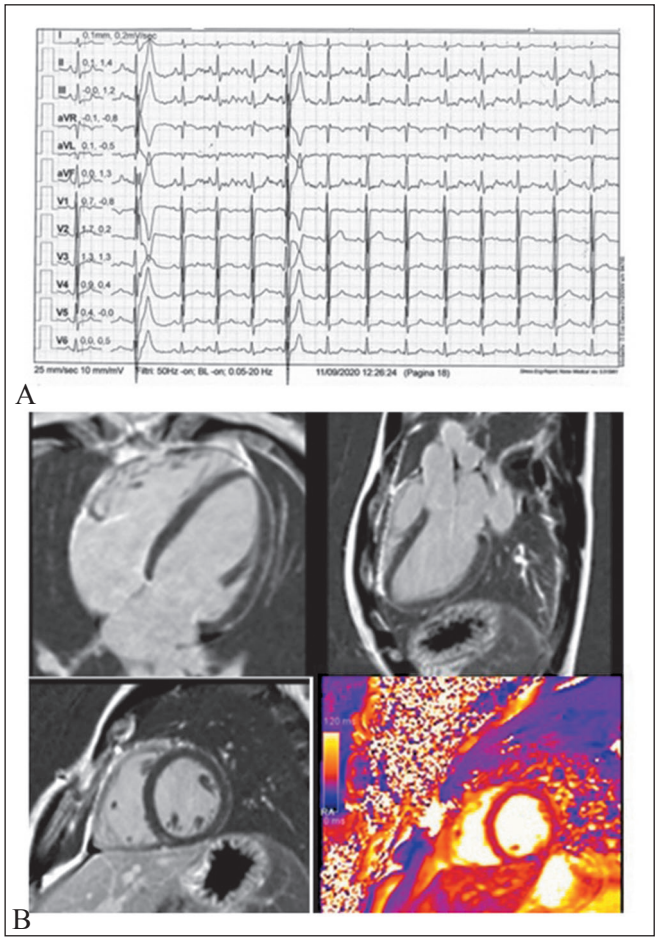

Figure 2.—Professional soccer player, 27-years-old. A) ECG strip of the exercise stress test showing frequent, isolated premature ventricular beats; B) cardiac magnetic resonance four-chamber, two chamber and short axis views showing subepicardial LGE in the mid-basal inferior wall; in the bottom right the T2 map short axis view showing limited edema.

myocardial LGE at the basal septum, minimal increase of T1 and T2 maps values compatible with limited edema/inflammatory changes" (Figure 2B). The athlete was disqualified from sports competition with a final diagnosis of COVID-19 related myopericarditis.

After a month of rest, he remained completely asymptomatic, he was re-evaluated with the same protocol. Blood tests, resting ECG, exercise stress test and echo were normal. The 24-hours ECG ambulatory monitoring showed a marked reduction of the PVBs burden (436/24 hours). Repeated CMR showed an almost completely regression of the alterations previously noticed and absence of LGE. For this reason, the athlete was readmitted to training and competitions with close follow-up (three months). Today, after 13 months of follow-up, rare PVBs are still present but the clinical picture remains stable, so the athlete is regularly attending training and competitions.

Case 2: a professional soccer player with marked abnormalities at the resting ECG

A 21-year-old professional soccer player tested positive for COVID-19 at a PCR nasal-pharyngeal swab during the routine screening of professional athletes. After nine days with mild symptoms (fatigue, myalgia, headache) he was declared healed. He then underwent the return-to-play protocol. The blood tests were normal, but the resting ECG showed diffuse and marked ST-elevation in inferior and precordial leads, with an evident ST-depression in aVR (Figure 3A). An ECG acquired 5 months before showed that the diffuse early repolarisation pattern was present but the ST-elevation was markedly lower and the depression in aVR was absent (Figure 3C). Transthoracic echo showed an increased signal in the lateral pericardium and a small inferior-apical pericardial effusion. The CMR confirmed a very thin sup-epicardial stria of LGE in the inferior and apical-lateral segments of the left ventricle, associated with mild anomalies of T1/T2-mapping and extracellular volumes in the same zones (Figure 3B). A diagnosis COVID-19 myopericarditis was made.

After a month of complete rest, the athlete has been re-evaluated. The blood samples were normal, the resting ECG showed a diffuse early repolarisation pattern with markedly reduced anomalies and disappearance of ST-depression in aVR (Figure 3D), a trace very similar to that of 6 months before. Echo was substantially normal and repeated CMR had normalized. No arrhythmias were found at exercise testing and 24-hour ambulatory ECG monitoring. The athlete was then considered healed and readmitted to training and competitions.

Case 3: a case of myopericarditis after mRNA-1279 COVID-19 vaccine

A 21-year-old male, with no past medical history, experienced fever (40 °C) on the same day of the second dose of mRNA-1273 COVID-19 vaccine, and chest pain exacerbated with breathing, three days later, for which he was admitted to the Emergency Department. On admission, he had normal vital signs with no fever. Nasopharyngeal SARS-CoV2 polymerase chain reaction was negative. The 12-lead resting electrocardiogram on arrival showed sinus rhythm, normal atrioventricular conduction, incomplete right bundle branch block and no ventricular repolarization abnormalities. The chest x-ray showed no significant find-

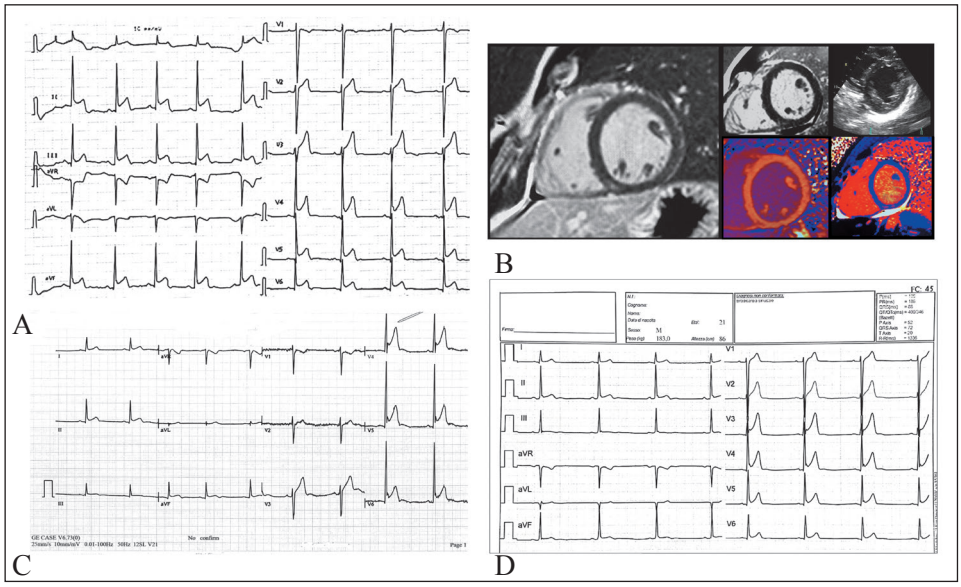

Figure 3.—A 21-year-old professional soccer player with mild COVID-19 infection. A) Resting ECG showing diffuse and marked ST-elevation in inferior and precordial leads, with an evident ST-depression in aVR; B) short axis cardiac magnetic resonance views showing left ventricle subepicardial LGE in the inferior and apical lateral segments and abnormalities on the T1 and T2 maps; on the upper right of panel B the transthoracic echo short axis showing increased echogenicity of the lateral pericardium; C) resting ECG performed 5 months before the post-COVID evaluation; D) resting ECG performed a month after the post-COVID-19 evaluation.

ings. Blood tests revealed a C-reactive protein =1.9 mg/dL (normal values <3 mg/dL) with white blood count within normal limits and increased levels of high-sensitivity troponin (366 ng/L, normal values <6 ng/L). Due to the clinical presentation and the elevation of high-sensitivity troponin, a complete transthoracic echo was performed. It showed a minimal pericardial effusion (2 mm) with hyperreflective pericardial layers, normal biventricular function and no significant heart valve disease. Due to the temporal correlation between the symptom onset and the second dose vaccine, the hypothesized diagnosis was acute myopericarditis as an adverse reaction to the mRNA-1273 COVID-19 vaccine.

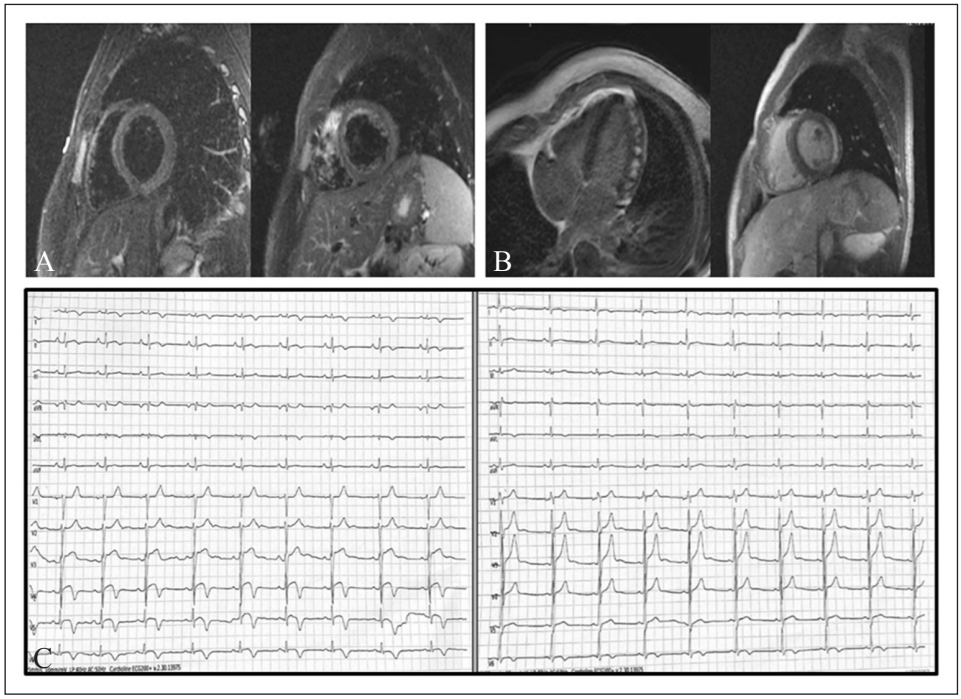

Figure 4.—A 21-year-old male admitted to the Emergency Department after the second dose of mRNA-1273 COVID-19 vaccine. A, B) CMR, which confirmed the diagnosis of acute myopericarditis, with ejection fraction 52%, evidence of myocardial edema in the mid-basal lateral wall and LGE in the subepicardial region of the basal inferolateral wall and mid-basal lateral wall; C) serial ECGs showed T-wave inversion in the lateral leads 2 days after the admission.

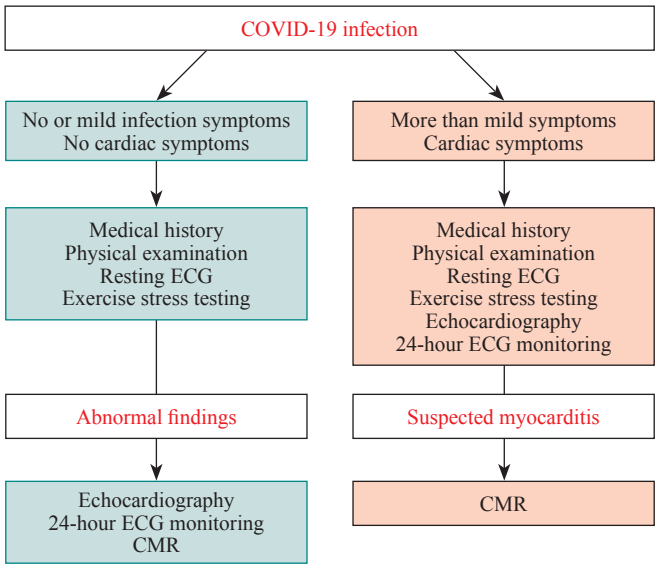

Figure 5.—Flow-chart of the suggested diagnostic tools to be used in athletes prior to the return to play after a COVID-19 infection.

Therefore, the patient underwent CMR, which confirmed the diagnosis of acute myopericarditis, with ejection fraction 52%, evidence of myocardial edema in the mid-basal lateral wall and LGE in the subepicardial region of the basal inferolateral wall and mid-basal lateral wall (Figure 4A, B). The disease course was benign. Due to the patient low-risk profile and the clear aetiology of the myocarditis, it was decided not to perform an endomyocardial biopsy. Nonsteroidal anti-inflammatory drugs were introduced to control chest pain, whereas colchicine was not introduced due to the prevalent myocardial involvement. Serial ECGs showed T-wave inversion in the lateral leads 2 days after the admission (Figure 4C). Blood tests revealed an initial increase in markers of myocardial injury (peak high-sensitivity troponin 1414 ng/L and isozyme creatin-kinase MB 50 ng/mL) and C-reactive protein levels (peak 2.16 mg/dL), with a decreasing trend until complete normalization before the hospital discharge. The patient was discharged on the 9th day of the in-hospital stay. As the patient was non-elite athlete, he will be re-evaluted before returning to play.

Conclusions

Myocarditis and pericarditis are reported in no or mildly symptomatic COVID-19 patient.[71] Symptoms did not always seem to correlate with cardiac involvement, although this latter is often present in patients with more-than-mild COVID-19 symptoms.[71] Therefore, cardiac evaluation of athletes after COVID-19 is recommended to exclude cardiac complication. The best diagnostic tools to be used in this setting remain to be determined. In athletes with no or mild symptoms during SARS-CoV-2 infection, in the absence of cardiac symptoms, a return-to-play screening based on medical history, physical examination, resting ECG, and exercise testing for ventricular arrhythmias seems to be reasonable. Echocardiography, performed by experienced physicians using strain imaging, ambulatory ECG monitoring, and eventually CMR should be performed in case of abnormal findings. Conversely, in case of more-than-mild symptoms during SARS-CoV-2 infection or in the presence of cardiac symptoms, the screening should be extended with the use of echocardiography and ambulatory ECG monitoring, with CMR performed in cases of suspected myocarditis (Figure 5). Spyrometry, blood testing and cardiopulmonary exercise-testing might be unnecessary in athletes who did not report COVID-19 respiratory-related symptoms.[34, 72] The same considerations should be applied to cases of typical symptoms after a dose of m-RNA-based vaccine.

Larger studies considering different populations of athletes are neded to validate a cardiovascular protocol for a safe return to play.

References

1. Pina A, Castelletti S. COVID-19 and Cardiovascular Disease: a Global Perspective. Curr Cardiol Rep 2021;23:135.

2. Castelletti S. A Shift on the Front Line. N Engl J Med 2020;382:e83.

3. Chilazi M, Duffy EY, Thakkar A, Michos ED. COVID and Cardiovascular Disease: What We Know in 2021. Curr Atheroscler Rep 2021;23:37.

4. Khawaja SA, Mohan P, Jabbour R, Bampouri T, Bowsher G, Hassan AM, *et al.* COVID-19 and its impact on the cardiovascular system. Open Heart 2021;8:e001472.

5. Van Hattum J, Spies J, Verwijs S, Verwoert G, Boekholdt S, Groenink M, *et al.* Post corona infection cardiac abnormalities and the risk for sudden cardiac death. Eur J Prev Cardiol 2021;28.

6. Kotecha T, Knight DS, Razvi Y, Kumar K, Vimalesvaran K, Thornton G, *et al.* Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. Eur Heart J 2021;42:1866–78.

7. Caforio AL. Receipt of mRNA Vaccine against COVID-19 and Myocarditis. N Engl J Med 2021;385:2189–90.

8. Bhatia RT, Marwaha S, Malhotra A, Iqbal Z, Hughes C, Börjesson M, *et al.* Exercise in the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) era: A Question and Answer session with the experts Endorsed by the section of Sports Cardiology & Exercise of the European Association of Preventive Cardiology (EAPC). Eur J Prev Cardiol 2020;27:1242–51.

9. Starekova J, Bluemke DA, Bradham WS, Eckhardt LL, Grist TM, Kusmirek JE, *et al.* Evaluation for Myocarditis in Competitive Student Athletes Recovering From Coronavirus Disease 2019 With Cardiac Magnetic Resonance Imaging. JAMA Cardiol 2021;6:945–50.

10. Löllgen H, Bachl N, Papadopoulou T, Shafik A, Holloway G, Von-

bank K, *et al.* Infographic. Clinical recommendations for return to play during the COVID-19 pandemic. Br J Sports Med 2021;55:344–5.

11. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, *et al.*; Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743–800.

12. D'Ascenzi F, Valentini F, Pistoresi S, Frascaro F, Piu P, Cavigli L, *et al.* Causes of sudden cardiac death in young athletes and non-athletes: systematic review and meta-analysis. Trends Cardiovasc Med 2022;;32:299–308.

13. Abou Hassan OK, Sheng CC, Wang TK, Cremer PC. SARS-CoV-2 Myocarditis: Insights Into Incidence, Prognosis, and Therapeutic Implications. Curr Cardiol Rep 2021;23:129.

14. Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, *et al.* Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. Eur Heart J 2020;41:3827–35.

15. Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. Cardiovasc Pathol 2021;50:107300.

16. Escher F, Pietsch H, Aleshcheva G, Bock T, Baumeier C, Elsaesser A, *et al.* Detection of viral SARS-CoV-2 genomes and histopathological changes in endomyocardial biopsies. ESC Heart Fail 2020;7:2440–7.

17. Hikmet F, Méar L, Edvinsson Å, Micke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. Mol Syst Biol 2020;16:e9610.

18. Tucker NR, Chaffin M, Bedi KC Jr, Papangeli I, Akkad AD, Arduini A, *et al.*; Human Cell Atlas Lung Biological Network; Human Cell Atlas Lung Biological Network Consortium Members. Myocyte-Specific Upregulation of ACE2 in Cardiovascular Disease: Implications for SARS-CoV-2-Mediated Myocarditis. Circulation 2020;142:708–10.

19. Sharma A, Garcia G Jr, Wang Y, Plummer JT, Morizono K, Arumugaswami V, *et al.* Human iPSC-Derived Cardiomyocytes Are Susceptible to SARS-CoV-2 Infection. Cell Rep Med 2020;1:100052.

20. Yiangou L, Davis RP, Mummery CL. Using Cardiovascular Cells from Human Pluripotent Stem Cells for COVID-19 Research: Why the Heart Fails. Stem Cell Reports 2021;16:385–97.

21. Evangelista FS. Physical Exercise and the Renin Angiotensin System: prospects in the COVID-19. Front Physiol 2020;11:561403.

22. Chung MK, Zidar DA, Bristow MR, Cameron SJ, Chan T, Harding CV 3rd, *et al.* COVID-19 and Cardiovascular Disease: From Bench to Bedside. Circ Res 2021;128:1214–36.

23. Centers for Disease Control and Prevention, COVID Data Tracker. [Internet]. Available from: https://covid.cdc.gov/covid-data-tracker/#demographicsovertime [cited 2022, Nov 16].

24. Rajpal S, Tong MS, Borchers J, Zareba KM, Obarski TP, Simonetti OP, *et al.* Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. JAMA Cardiol 2021;6:116–8.

25. Vago H, Szabo L, Dohy Z, Merkely B. Cardiac Magnetic Resonance Findings in Patients Recovered From COVID-19: Initial Experiences in Elite Athletes. JACC Cardiovasc Imaging 2021;14:1279–81.

26. Moulson N, Petek BJ, Drezner JA, Harmon KG, Kliethermes SA, Patel MR, *et al.*; Outcomes Registry for Cardiac Conditions in Athletes Investigators. SARS-CoV-2 Cardiac Involvement in Young Competitive Athletes. Circulation 2021;144:256–66.

27. Gervasi SF, Pengue L, Damato L, Monti R, Pradella S, Pirronti T, *et al.* Is extensive cardiopulmonary screening useful in athletes with previous asymptomatic or mild SARS-CoV-2 infection? Br J Sports Med 2021;55:54–61.

28. Clark DE, Parikh A, Dendy JM, Diamond AB, George-Durrett K, Fish FA, *et al.* COVID-19 Myocardial Pathology Evaluation in Athletes With Cardiac Magnetic Resonance (COMPETE CMR). Circulation 2021;143:609–12.

29. Małek ŁA, Marczak M, Miłosz-Wieczorek B, Konopka M, Braksator W, Drygas W, *et al.* Cardiac involvement in consecutive elite athletes recovered from Covid-19: A magnetic resonance study. J Magn Reson Imaging 2021;53:1723–9.

30. Daniels CJ, Rajpal S, Greenshields JT, Rosenthal GL, Chung EH, Terrin M, *et al.*; Big Ten COVID-19 Cardiac Registry Investigators. Prevalence of Clinical and Subclinical Myocarditis in Competitive Athletes With Recent SARS-CoV-2 Infection: Results From the Big Ten COVID-19 Cardiac Registry. JAMA Cardiol 2021;6:1078–87.

31. Brito D, Meester S, Yanamala N, Patel HB, Balcik BJ, Casaclang-Verzosa G, *et al.* High Prevalence of Pericardial Involvement in College Student Athletes Recovering From COVID-19. JACC Cardiovasc Imaging 2021;14:541–55.

32. Hendrickson BS, Stephens RE, Chang JV, Amburn JM, Pierotti LL, Johnson JL, *et al.* Cardiovascular Evaluation After COVID-19 in 137 Collegiate Athletes: Results of an Algorithm-Guided Screening. Circulation 2021;143:1926–8.

33. Martinez MW, Tucker AM, Bloom OJ, Green G, DiFiori JP, Solomon G, *et al.* Prevalence of Inflammatory Heart Disease Among Professional Athletes With Prior COVID-19 Infection Who Received Systematic Return-to-Play Cardiac Screening. JAMA Cardiol 2021;6:745–52.

34. Cavigli L, Frascaro F, Turchini F, Mochi N, Sarto P, Bianchi S, *et al.* A prospective study on the consequences of SARS-CoV-2 infection on the heart of young adult competitive athletes: implications for a safe return-to-play. Int J Cardiol 2021;336:130–6.

35. Szabó L, Juhász V, Dohy Z, Fogarasi C, Kovács A, Lakatos BK, *et al.* Is cardiac involvement prevalent in highly trained athletes after SARS-CoV-2 infection? A cardiac magnetic resonance study using sex-matched and age-matched controls. Br J Sports Med 2022;56:553–60.

36. Cavigli L, Cillis M, Mochi V, Frascaro F, Mochi N, Hajdarevic A, *et al.* SARS-CoV-2 infection and return to play in junior competitive athletes: is systematic cardiac screening needed? Br J Sports Med 2021;56:264–70.

37. D'Ascenzi F, Castelletti S, Adami PE, Cavarretta E, Sanz-de la Garza M, Maestrini V, *et al.* Cardiac screening prior to return to play after SARS-CoV-2 infection: focus on the child and adolescent athlete: A Clinical Consensus Statement of the Task Force for Childhood Health of the European Association of Preventive Cardiology. Eur J Prev Cardiol 2022;15 29(16):2920–2124.

38. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, *et al.* Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020;5:1265–73.

39. Corrado D, Drezner JA, D'Ascenzi F, Zorzi A. How to evaluate premature ventricular beats in the athlete: critical review and proposal of a diagnostic algorithm. Br J Sports Med 2020;54:1142–8.

40. Phelan D, Kim JH, Elliott MD, Wasfy MM, Cremer P, Johri AM, *et al.* Screening of Potential Cardiac Involvement in Competitive Athletes Recovering From COVID-19: An Expert Consensus Statement. JACC Cardiovasc Imaging 2020;13:2635–52.

41. Schellhorn P, Klingel K, Burgstahler C. Return to sports after COVID-19 infection. Eur Heart J 2020;41:4382–4.

42. Wilson MG, Hull JH, Rogers J, Pollock N, Dodd M, Haines J, *et al.* Cardiorespiratory considerations for return-to-play in elite athletes after COVID-19 infection: a practical guide for sport and exercise medicine physicians. Br J Sports Med 2020;54:1157–61.

43. Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome. Circulation 2020;141:1903–14.

44. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, *et al.* Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020;5:819–24.

45. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, *et al.*; European Society of Cardiology Working Group on Myo-

cardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636–48, 2648a–2648d.

46. Zhang L, Wang B, Zhou J, Kirkpatrick J, Xie M, Johri AM. Bedside Focused Cardiac Ultrasound in COVID-19 from the Wuhan Epicenter: The Role of Cardiac Point-of-Care Ultrasound, Limited Transthoracic Echocardiography, and Critical Care Echocardiography. J Am Soc Echocardiogr 2020;33:676–82.

47. Picard MH, Weiner RB. Echocardiography in the Time of COVID-19. J Am Soc Echocardiogr 2020;33:674–5.

48. Huang G, Vengerovsky A, Morris A, Town J, Carlbom D, Kwon Y. Development of a COVID-19 Point-of-Care Ultrasound Protocol. J Am Soc Echocardiogr 2020;33:903–5.

49. Citro R, Pontone G, Bellino M, Silverio A, Iuliano G, Baggiano A, *et al.* Role of multimodality imaging in evaluation of cardiovascular involvement in COVID-19. Trends Cardiovasc Med 2021;31:8–16.

50. Cau R, Bassareo P, Saba L. Cardiac Involvement in COVID-19-Assessment with Echocardiography and Cardiac Magnetic Resonance Imaging. SN Compr Clin Med 2020;2:845–51.

51. Rademakers FE, Rogers WJ, Guier WH, Hutchins GM, Siu CO, Weisfeldt ML, *et al.* Relation of regional cross-fiber shortening to wall thickening in the intact heart. Three-dimensional strain analysis by NMR tagging. Circulation 1994;89:1174–82.

52. Cavarretta E, D'Angeli I, Giammarinaro M, Gervasi S, Fanchini M, Causarano A, *et al.* Cardiovascular effects of COVID-19 lockdown in professional Football players. Panminerva Med 2021. [Epub ahead of print].

53. Di Bella G, de Gregorio C, Minutoli F, Pingitore A, Coglitore S, Arrigo F, *et al.* Early diagnosis of focal myocarditis by cardiac magnetic resonance. Int J Cardiol 2007;117:280–1.

54. Sandoval Y, Januzzi JL Jr, Jaffe AS. Cardiac Troponin for Assessment of Myocardial Injury in COVID-19: JACC Review Topic of the Week. J Am Coll Cardiol 2020;76:1244–58.

55. Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, *et al.* Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2022;28:410–22.

56. Mascia G, Pescetelli F, Baldari A, Gatto P, Seitun S, Sartori P, *et al.* Interpretation of elevated high-sensitivity cardiac troponin I in elite soccer players previously infected by severe acute respiratory syndrome coronavirus 2. Int J Cardiol 2021;326:248–51.

57. Zorzi A, Perazzolo Marra M, Rigato I, De Lazzari M, Susana A, Niero A, *et al.* Nonischemic Left Ventricular Scar as a Substrate of Life-Threatening Ventricular Arrhythmias and Sudden Cardiac Death in Competitive Athletes. Circ Arrhythm Electrophysiol 2016;9:e004229.

58. Vio R, Zorzi A, Corrado D. Myocarditis in the Athlete: Arrhythmogenic Substrates, Clinical Manifestations, Management, and Eligibility Decisions. J Cardiovasc Transl Res 2020;13:284–95.

59. Zorzi A, Vessella T, De Lazzari M, Cipriani A, Menegon V, Sarto G, *et al.* Screening young athletes for diseases at risk of sudden cardiac death: role of stress testing for ventricular arrhythmias. Eur J Prev Cardiol 2020;27:311–20.

60. Cipriani A, Zorzi A, Sarto P, Donini M, Rigato I, Bariani R, *et al.* Predictive value of exercise testing in athletes with ventricular ectopy evaluated by cardiac magnetic resonance. Heart Rhythm 2019;16:239–48.

61. Crescenzi C, Zorzi A, Vessella T, Martino A, Panattoni G, Cipriani A, *et al.* Predictors of Left Ventricular Scar Using Cardiac Magnetic Resonance in Athletes With Apparently Idiopathic Ventricular Arrhythmias. J Am Heart Assoc 2021;10:e018206.

62. Komici K, Bianco A, Perrotta F, Dello Iacono A, Bencivenga L, D'Agnano V, *et al.* Clinical Characteristics, Exercise Capacity and Pulmonary Function in Post-COVID-19 Competitive Athletes. J Clin Med 2021;10:3053.

63. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, *et al.* Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med 2021;385:1078–90.

64. Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, *et al.* Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med 2021;385:2140–9.

65. Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and Pericarditis After Vaccination for COVID-19. JAMA 2021;326:1210–2.

66. Bozkurt B, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. Circulation 2021;144:471–84.

67. Sinagra G, Porcari A, Merlo M, Barillà F, Basso C, Ciccone MM, *et al.* [Myocarditis and pericarditis following mRNA COVID-19 vaccination. Expert opinion of the Italian Society of Cardiology]. G Ital Cardiol (Rome) 2021;22:894–9.

68. Kadkhoda K. Post RNA-based COVID vaccines myocarditis: proposed mechanisms. Vaccine 2022;40:406–7.

69. Abu Mouch S, Roguin A, Hellou E, Ishai A, Shoshan U, Mahamid L, *et al.* Myocarditis following COVID-19 mRNA vaccination. Vaccine 2021;39:3790–3.

70. Law YM, Lal AK, Chen S, Čiháková D, Cooper LT Jr, Deshpande S, *et al.*; American Heart Association Pediatric Heart Failure and Transplantation Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young and Stroke Council. Diagnosis and Management of Myocarditis in Children: A Scientific Statement From the American Heart Association. Circulation 2021;144:e123–35.

71. Kim JH, Levine BD, Phelan D, Emery MS, Martinez MW, Chung EH, *et al.* Coronavirus Disease 2019 and the Athletic Heart: Emerging Perspectives on Pathology, Risks, and Return to Play. JAMA Cardiol 2021;6:219–27.

72. Hwang CE, Kussman A, Christle JW, Froelicher V, Wheeler MT, Moneghetti KJ. Findings From Cardiovascular Evaluation of National Collegiate Athletic Association Division I Collegiate Student-Athletes After Asymptomatic or Mildly Symptomatic SARS-CoV-2 Infection. Clin J Sport Med 2022;32:103–7.

Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Silvia Castelletti, Paolo Zeppilli, Luigi Sciarra have given substantial contributions to the conception or the design of the manuscript; Salvatore Gervasi, Vincenzo Palmiri, Monica Tiberi, Lucio Mos, Flavio D'Ascenzi, Luigi Sciarra to acquisition of the cases. All authors have participated to drafting the manuscript, Silvia Castelletti, Salvatore Gervasi, Paolo Zeppilli, Luigi Sciarra revised it critically. All authors read and approved the final version of the manuscript.

Acknowledgements
In memory of Salvo, a brilliant colleague and amazing person who was taken from us far too soon.

History
Article first published online: September 30, 2022. - Manuscript accepted: September 23, 2022. - Manuscript revised: July 22, 2022. - Manuscript received: March 31, 2022.