Original Research

Prevalence and Diagnostic Significance of De-novo 12-lead ECG Changes

After COVID-19 Infection in Elite Soccer Players

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Abstract

Background and Aim: The efficacy of pre- and post-COVID-19 infection 12-lead electrocardiograms (ECGs) for identifying athletes with myopericarditis has never been reported. We aimed to assess the prevalence and significance of de-novo ECG changes following COVID-19 infection.

Methods: In this multicentre observational study, between March 2020–May 2022, we evaluated consecutive athletes with COVID-19 infection. Athletes exhibiting de-novo ECG changes underwent cardiovascular magnetic resonance (CMR) scans. One club mandated CMR scans for all players (n=30) following COVID-19 infection, despite the absence of cardiac symptoms or *de-novo* ECG changes.

Results: 511 soccer players (median age 21-years, IQR:18-26-years) were included. 17 (3%) athletes demonstrated de-novo ECG changes, which included, reduction in T-wave amplitude in the inferior and lateral leads (n=5), inferior leads (n=4) and lateral leads (n=4); inferior T-wave inversion (n=7), and ST-segment depression (n=2). 15 (88%) athletes with de-novo ECG changes revealed evidence of inflammatory cardiac sequelae. All 30 athletes who underwent a mandatory CMR scan had normal findings. Athletes revealing de-novo ECG changes, had a higher prevalence of cardiac symptoms (71% v 12%;p<0.0001) and longer median symptom duration (5-days, IQR:3-10) compared with athletes without de-novo ECG changes (2-days, IQR:1-3;p<0.001). Among athletes without cardiac symptoms, the additional yield of de-novo ECG changes to detect cardiac inflammation was 20%.

Conclusions: 3% of athletes demonstrated de-novo ECG changes post COVID-19 infection, of which 88% were diagnosed with cardiac inflammation. Most affected

athletes exhibited cardiac symptoms; however de-novo ECG changes contributed to

a diagnosis of cardiac inflammation in 20% of athletes without cardiac symptoms.

Clinical Perspective

What is new?

1. The efficacy of pre- and post-COVID-19 infection 12-lead electrocardiograms (ECGs) for identifying athletes with myopericarditis has never been reported.

2. De-novo ECG patterns following COVID-19 infection (3%) characterised by anomalies in the inferior and lateral leads including low amplitude T-waves, flat T-waves, or inverted T-waves identify athletes with cardiac inflammation (88%) on cardiovascular magnetic resonance (CMR) imaging.

3. Whereas most affected athletes express cardiac symptoms, such de-novo ECG changes identify an additional 20% athletes presenting with non-cardiac symptoms.

What are the clinical implications?

1. The presence of cardiac symptoms and/or *de-novo* ECG changes offer a greater diagnostic yield to detect cardiac inflammation in comparison to offering a mandatory CMR, irrespective of symptomatology or ECG findings.

2. Despite a different approach, our prevalence of inflammatory cardiac sequelae (2.9%) following COVID infection is similar to data reported in North American professional and collegiate athletes.

3. Our approach is a cheap and pragmatic method of identifying athletes with sub-clinical myocarditis in a setting where serial cardiac assessments including ECGs are conducted on an annual basis and may also be applicable to athletes playing at the grass-roots level.

Introduction

Observational studies, reveal that up to 30% of individuals hospitalised for severe COVID-19 infection show biochemical evidence of myocardial injury.[1,2] Old age, obesity, the presence of multiple risk factors for atherosclerosis and concomitant cardiac comorbidity are recognised risk factors, suggesting that plaque rupture is an important cause of myocardial injury, however it is also well established that COVID-19 infection predisposes to myocarditis.[2,3] Whilst caution must be advised when extrapolating these data to the younger and generally healthier athletic population (figure 1), a diagnosis of myocarditis, has serious implications in athletes due to its association with fatal arrhythmias during vigorous exercise.[4–6]

Reports from large cohorts of collegiate and professional athletes in the United States, indicate that the prevalence of myocarditis following mild to moderate COVID-19 infection is 0.6-3%.[7,8] These figures are a justified incentive for identifying affected athletes as evidenced by several consensus-based evaluation protocols for infected athletes in North America and Europe.[9–15] Given its widespread availability, the inclusion of a 12-lead electrocardiogram (ECG) is common to all protocols,[9–14] however, a single cross-sectional ECG is problematic because several physiological repolarisation changes affecting the J-point, ST-segment and T wave are also common manifestations in individuals with myopericarditis.[16] Most elite sporting organisations, however, recommend annual assessments in athletes which provides an opportunity to investigate the significance of de-novo electrical changes, during or shortly after viral infection.

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The aim of our study was to report on the prevalence and diagnostic significance of de-novo ECG patterns following COVID-19 infection in a well-defined cohort of elite soccer players in the English, Dutch and Brazilian league.

Methods

Setting

The English, Dutch and Brazilian Football Associations mandate at least an annual cardiac assessment in soccer players aged 16 years old and above. Our sports cardiology units, led by senior authors AK, AM, AV, DR, HJ, MP, RC, RS and SS serve several clubs and maintain records of serial assessments for all athletes. During the on-going COVID-19 pandemic, several clubs requested a minimum of a 12-lead ECG in athletes with confirmed COVID-19 infection. We compared ECGs performed during the last assessment, prior to testing positive for COVID-19 infection with ECGs performed following COVID-19 infection. The study was given ethical approval by the St. George's Research Ethics Committee (SGREC) 2021.0139. Written informed consent was obtained from each athlete, in accordance with the Football Association (FA) governance department, respective sporting bodies and team management in the Netherlands and Brazil, which acknowledge that anonymised clinical information may be used for medical research purposes.

Subjects

Fully anonymised data from 511 athletes was collected from 9 sports cardiologists serving 36 elite soccer clubs between 1st March 2020 and 15th May 2022 (figure 2). All athletes who were referred to a sports cardiologist following testing positive for COVID-19 infection on polymerase chain reaction (PCR) and/or antibody test and in whom a previous ECG was available were included. All previous ECGs were reported in accordance with the International recommendations for ECG interpretation in athletes.[16] Athletes with a previously abnormal baseline ECG were excluded (n=6). These included athletes who were under regular surveillance due to marked repolarisation changes indicative of an overt cardiomyopathic phenotype. All pre-COVID-19 ECGs were performed during the routine cardiac evaluation at the onset of the soccer season.

All athletes underwent an initial clinical evaluation including a clinical history and 12-lead ECG. The clinical history pertained to the presence and duration of cardiovascular symptoms, as well as a comprehensive systems review. A standard 12-lead ECG was conducted in a supine position at a paper speed of 25 mm/s and voltage of 10mm/mV.[17]

De-novo ECG patterns: criteria for an abnormal post COVID-19 ECG

The International recommendations for ECG interpretation recommend further investigations in athletes with several anomalies that may reflect myopericarditis such as atrioventricular (AV) block, left bundle branch block, ST-segment depression, T-wave inversion (TWI) and ventricular extrasystoles.[16] Given that some repolarisation changes overlap between myopericarditis and athlete's heart, we also considered the following ECG patterns as abnormal if they were not detected on the

pre-COVID-19 infection ECG: PR-segment depression, new J-point and ST segment elevation (≥0.2mV in the precordial leads and ≥0.1mV in the limb leads), low QRS voltages, complete right bundle branch block, QRS fragmentation, new ST-segment depression, new T-wave inversion, biphasic T-waves and a reduction in the T-wave amplitude by 50% or T-wave flattening.

Further investigation

Athletes with de-novo ECG changes, underwent transthoracic echocardiography (TTE) and cardiovascular magnetic resonance (CMR) imaging. One institution included CMR imaging in all athletes, with COVID-19 infection, irrespective of non-cardiac symptoms, mild disease severity or the absence of de-novo ECG changes.

Transthoracic echocardiography (TTE)

TTE was performed by sonographers accredited by the British Society of Echocardiography (BSE) and/or the European Association of Cardiovascular Imaging (EACVI). Cardiac measurements and interpretation were conducted in accordance with a standardised minimum dataset and a joint policy statement of the BSE and Cardiac Risk in the Young (CRY), which accounts for physiological cardiac adaptations to vigorous exercise.[18]

Cardiovascular magnetic resonance (CMR) imaging

CMR imaging was considered as the gold-standard non-invasive modality to assess for myocarditis. Scans were performed either using a 1.5-tesla or 3-tesla scanner with ECG-synchronised cine acquisitions. Sequences included: multiple white blood steady-state free precession (SSFP) images and cines, multiple turbo spin echo

(TSE) black blood images, T2 short tau inversion recovery (STIR) images, tissue characterisation and delayed enhancement images following gadolinium. In athletes with suspected acute or active myocardial inflammation, we applied the Updated Lake Louise Imaging criteria.[19] All scans were performed in large volume tertiary centres and reported by experts formally accredited in CMR with particular expertise in inherited cardiac conditions and sports cardiology. Furthermore, most scans were dual reported by at least two experts in the field.

Inflammatory cardiac sequelae

To facilitate onward management and risk stratification, in a cohort of ostensibly healthy athletes, the authors considered the following clinical definitions to indicate inflammatory cardiac sequelae:

Acute pericarditis: the presence of at least two of the following criteria: (i) chest pain – typically sharp and pleuritic, alleviated by sitting up and leaning forward; (ii) ECG changes – with new PR depression or ST elevation; and (iii) the presence of a pericardial effusion, either using TTE or CMR imaging.

Definitive myocarditis: the presence of at least three of the following criteria (i) cardiac symptoms; (ii) where performed, an elevated serum cardiac troponin; (iii) the presence of de-novo ECG changes (iv) regional wall motion abnormalities or impaired left ventricular function (LVEF <50%) on TTE; and (v) CMR findings consistent with an episode of active inflammation.

Possible myocarditis: the presence of at least three of the following criteria (i) cardiac symptoms; (ii) where performed, an elevated serum cardiac troponin; (iii) the presence of de-novo ECG changes (iv) regional wall motion abnormalities or

impaired left ventricular function (LVEF <50%) on TTE but where an athlete did not undergo CMR, or in absence of acute inflammation on CMR.

Probable myocarditis: the presence of at least three of the following criteria (i) cardiac symptoms; (ii) where performed, an elevated serum cardiac troponin; (iii) the presence of de-novo ECG changes (iv) regional wall motion abnormalities or impaired left ventricular function (LVEF <50%) on TTE; and (v) CMR findings consistent with subepicardial or mid-wall scar.

Statistical analysis

Data are expressed as medians (IQRs) or percentages as appropriate and analysed with Microsoft Excel version 16.61.1 and Statistica 13.1. Comparison between groups was performed using the Student t-test or U-Mann Whitney test for continuous variables, the decision on the test used was based on the outcome of the Shapiro-Wilk test for data distribution. The chi-square test was used for categorical variables, with the Fisher exact test considered in the cases with more than 20% of cells having expected frequencies <5. Statistical significance was defined as $p<0.05$.

Results

The median age of athletes was 21 years; interquartile range [IQR]: 18 to 26 years, of which 88% were male. The cohort was ethnically diverse consisting of 58% white athletes, 18% black athletes and 17% athletes of mixed ethnicity. In accordance with public health guidance at the time of the study, following a mandatory 7 to 10-day period of isolation, the median time for a sports cardiology specialist review following a positive COVID-19 PCR/antibody test was of 11 days (IQR: 10-14 days). From

February 2022, the legal requirements around self-isolation for individuals who tested positive for coronavirus was abolished in the United Kingdom, which shortened the gap between an athlete testing positive for COVID-19 infection and being reviewed by a sports cardiologist was a median of 7 days (IQR: 6-9 days). The median duration of illness was 2 days (IQR: 1-3 days). The median time interval between the pre and post COVID-19 ECG was 239 days (IQR: 164-462 days).

494 (97%) athletes had a normal post COVID-19 ECG. Of these, 4 (0.8%) reported persistent cardiac symptoms, with a median duration of illness of 12 days (IQR: 9-17 days) and downstream investigations, including CMR imaging resulted in a diagnosis of pericarditis in all 4 athletes. None of the athletes in this group revealed overt features of definite, probable, or possible myocarditis.

17 (3%) athletes demonstrated de-novo ECG changes, which included, a reduction in T-wave amplitude by 50% in ≥ 2 contiguous leads with the preceding R-wave taller than 0.3 mV in the inferior and lateral leads (n=5), isolated inferior leads (n=4) and isolated lateral leads (n=4); new T-wave inversion in the inferior leads (n=7), inferior and lateral leads (n=1), anterior and lateral leads (n=1) and isolated lateral leads (n=1); ST-segment depression (n=2); biphasic T-waves (n=2); new J-point and ST-segment elevation ≥ 0.2mV in the precordial leads (n=1) and new J-point and ST-segment elevation ≥ 0.1mV in the limb leads (n=2) (figure 2 and supplementary file table 1). The median time from a positive PCR to a 12-lead ECG in individuals who revealed de-novo ECG changes was 13 days (IQR: 10-15 days).

15 (88%) athletes with de-novo ECG changes were diagnosed with inflammatory cardiac sequelae including pericarditis (n=5), probable healed myocarditis (n=3),

definitive myocarditis (n=3), possible myocarditis (n=2) and healed myocarditis (n=2) (supplementary file table 1, figures 2-4). These changes occurred in individuals who had a median illness duration of 7 days (IQR: 4-14 days) and 12 (80%) of the athletes reported cardiac symptoms. 2 (0.4%) athletes demonstrated new inferior TWI (n=1), and inferolateral T wave flattening (n=1) showed no evidence of inflammatory cardiac changes on downstream testing. The overall prevalence of inflammatory cardiac sequelae in the cohort based on de-novo ECG changes was 3%. Among athletes without cardiac symptoms, the additional yield of de-novo ECG changes to detect cardiac inflammation was 20% (n=3; supplementary file table 1: athlete number 4, 5, and 7 demonstrated the presence of late gadolinium enhancement, LGE).

12 athletes identified with inflammatory cardiac sequelae, demonstrated resolution of de-novo ECG changes (supplementary file table 1, Figure 3 and 4); the ECG changes persisted in 1 athlete with healed myocarditis; and follow up ECG were not available in 2 players who moved clubs.

None of the 30 asymptomatic or paucisymptomatic athletes who were investigated with a CMR despite a normal ECG, revealed cardiac inflammation compared with 88% of the athletes with de-novo ECG changes (Table 1 and Table 2). Athletes revealing de-novo ECG changes had a longer symptom duration (median 5 days [IQR 3-10 days]) compared to athletes undergoing mandatory CMR assessment (median 0 days (asymptomatic) [IQR 0-3 days]; p<0.0001. There were no significant differences in quantitative CMR parameters between athletes with de-novo ECG

changes and athletes who underwent mandatory CMR despite the absence of

cardiac symptoms or abnormal ECG (Table 1).

	Athletes undergoing mandatory CMR assessment (n=30)	Athletes demonstrating de-novo ECG changes undergoing CMR assessment (n=17)	P value
Age	26 (19-30)	22 (19-25)	0.094
BSA (m2)	2 (1.9-2.1)	2 (1.9-2.1)	0.861
Symptom duration (days; 0=asymptomatic)	0 (0-3)	5 (3-10)	0.0001*
Positive PCR to ECG	11 (11-11)	12 (10-14)	0.298
Positive PCR to CMR	11 (11-11)	15 (11.5-19.5)	0.005*
LV MWT (mm)	10 (9-10)	9 (9-11)	0.770
LV EF (%)	59 (57-62)	60 (57-64.3)	0.415
LV mass indexed (g/m2)	72 (54-83)	82 (65-93)	0.094
RV EF (%)	53 (51-60)	58 (51-62.5)	0.179
Presence of inflammatory cardiac sequalae	0	15	

Table 1: Comparison of CMR data between athletes demonstrating de-novo

ECG changes and athletes undergoing a mandatory CMR.

Values are expressed as median (IQR); *P value <0.05 deemed statistically

significant

BSA: body surface area; CMR: cardiac magnetic resonance; ECG:

electrocardiogram; LVEF: left ventricular ejection fraction; LVMWT: left ventricle

maximal wall thickness; PCR: polymerase chain reaction; RVEF: right ventricular

ejection fraction.

Total cohort, n=511	CV symptoms*	De-novo ECG changes	Cardiac MRI
1) No de-novo ECG changes, n=494 (97%)	Persistent symptoms: n=4 (0.8%) None: n=490 (99%)	None: n=494 (97%)	4 athletes with persistent CV symptoms (median duration 12 days [IQR: 9-17 days]) had abnormal CMRs and were diagnosed with pericarditis.
(a) Includes, mandatory CMR group n=30 (6%)	None	None	All 30 athletes underwent a mandatory CMR: normal findings.
2) De-novo ECG changes group, n=17 (3%)	Yes: n=12 (71%) No: n=5 (29%)	Yes: n=17 (3%)	All underwent CMR ○ Normal: n=2 (12%) ○ Abnormal: n=15 (88%); all diagnosed with inflammatory cardiac sequelae (12 reported CV symptoms; 3 reported no CV symptoms)

Table 2 Summary of cardiovascular symptom burden, de-novo ECG changes and MRI findings in overall cohort. CMRI: cardiovascular magnetic resonance imaging; CV: cardiovascular; ECG: electrocardiogram; IQR: interquartile range. *The clinical assessment as a minimum included a comprehensive history, systems review, examination, and electrocardiogram. Further onward investigations were performed based on the respective sports cardiologists, club or team doctor policy.

Follow-up

All athletes with confirmed cardiac inflammation were appraised by experts in the field. Conventional risk-stratification included a maximal exercise stress test,

ambulatory Holter monitor, prolonged arrhythmia monitoring for up to 2-weeks in certain cases, and close surveillance by the club doctors and respective sports cardiologist. None of the athletes revealed significant impairment in functional and haemodynamic status on exercise testing and arrhythmia monitoring did not reveal any evidence of complex ventricular arrhythmia or myocardial ischaemia.

During a median follow up 270 days (IQR: 133-487 days), there were no adverse cardiac events among infected athletes in the entire cohort. All athletes identified with cardiac inflammation returned to play following conventional risk stratification tests and tailored exercise prescriptions without adverse events over a median follow up period of 479 days (IQR: 268-520 days).

Discussion

The resting 12-lead ECG has a low sensitivity for identifying individuals with myocarditis which is estimated at <50%.[20,21] Amongst athletes, the overlap between physiological repolarization changes and myocarditis indicates that the specificity of the ECG may be even lower than the sensitivity. However, the precise significance of de-novo ECG patterns following COVID-19 infection in athletes, has not been investigated. Our study revealed that 3% of professional soccer players revealed de-novo ECG changes, of which, 88% demonstrated features compatible with inflammatory cardiac sequelae.

ECG changes have been reported with other viral infections and may have prognostic relevance. Almost 30% of hospitalized patients with H1N1 influenza virus

revealed anomalous patterns including T-wave inversion and ST-segment depression.[22] Specific ECG changes such as diminished QRS amplitude in COVID-19 infection or influenza infected hospitalized patients with pre-existing comorbidities was independently observed to precede clinical decompensation and were associated with an increased mortality.[23,24] As far as we are aware, this is the first study reporting the prevalence and significance of de-novo ECG changes in ostensibly healthy young athletes with COVID-19 infection of mild to moderate severity.

The most common ECG alterations following infection affected the inferior and lateral leads and are consistent with the typical cardiac MRI findings in individuals with myocarditis, who demonstrate a predilection for myocardial scar localised to the basal inferolateral wall.[25]

Only 3 of our athletes fulfilled the Updated Lake Louise criteria for acute myocardial inflammation, however it is noteworthy that these criteria were derived from a cohort of acutely unwell patients, where the CMR scan was performed in a timely fashion to detect myocardial oedema. In contrast, our athletes had mild or subclinical inflammation where the temporal relationship between confirmation of infection and CMR findings was probably too long to reveal acute inflammation but identified residual scar in most cases.

In the absence of a baseline CMR, it may be argued that the scar tissue may have been a compensatory response to decades of vigorous exercise.[26,27] However, we did not find any evidence of inflammation or scar in 30 asymptomatic or

paucisymptomatic athletes who underwent a mandatory CMR despite an unchanged ECG.

Despite a different approach to the triad testing in North American studies in athletes[7], which included troponin measurements, our prevalence (2.9%) of inflammatory cardiac sequelae post COVID-19 infection, based on similar disease definitions[7,8,28] is similar to the upper limit of the prevalence reported by from American studies (3%).

Most athletes (80%) exhibiting de-novo ECG changes revealed symptoms compatible with myopericarditis and were symptomatic for a median of 7 days (IQR: 4-14 days). Our observations are in keeping with North American and European recommendations which indicate that cardiac symptoms should be the main driver for selecting athletes for cardiac investigations post infection.[10,28] Although based on a small number of athletes, we noted that a minority of athletes who did not report cardiac symptoms but revealed de-novo ECG changes showed evidence of myocardial inflammation. It is well recognised from autopsy series that coryzal symptoms have predominated in a large proportion of decedents with viral myocarditis.[29]

The uncertainty surrounding the current pandemic dictates that some sporting organisations may continue to investigate asymptomatic athletes with COVID-19 infection. Our study shows that comparison of pre-and post-COVID-19 ECGs is a

cheap and effective method for detecting asymptomatic athletes with cardiac inflammation and may also be applicable to athletes playing at the grass-roots level.

Our approach raises concern about the possibility of false positive ECG results, however, our observations revealed that only 2 athletes (12%) with de-novo ECG changes failed to demonstrate any evidence of cardiac inflammation during subsequent investigation. A recent study which applied the International criteria for ECG interpretation in athletes[16], reported that as many as 4% of 378 collegiate athletes in whom pre and post COVID-19 ECGs were available revealed abnormalities following COVID-19 despite normal cardiac imaging[30]. The precise significance of the ECG abnormalities in this cohort is still unclear since only 22% of athletes with new ECG changes underwent CMR as opposed to all our athletes.

In our study, during a median follow up period of 270 days (IQR: 133-487 days) there were no adverse outcomes which is reassuring, though long-term studies are required to ascertain the outcomes in athletes with myocardial inflammation post-COVID-19 infection.

Limitations

Our study has several limitations which warrant mention. The cohort of interest, notably, athletes with de-novo ECG changes was relatively small and reflects the low prevalence of myocarditis in athletes infected with COVID-19. It is possible that some of the de-novo ECG changes reflected change in variation in training intensity. However, most of our pre COVID-19 ECGs were performed as part of routine cardiac evaluations just prior to the onset of the season when players are extremely conditioned. The absence of cardiac inflammation in equal numbers of athletes with

normal ECGs who underwent CMR suggests that the de-novo ECG changes we observed were a genuine representation of cardiac pathology. Importantly, we did not rely on inflammatory markers and/or biomarkers of cardiac damage and systemic inflammation. In view of public health measures to curtail viral spread, which largely included a mandatory period of self-isolation for athletes, by which time we were mindful that measures of inflammation might have normalised. Furthermore, many of our asymptomatic athletes continued to partake in regular physical activity whilst isolating which is a recognised cause of transient elevation in their serum cardiac troponin.

Conclusions

3% of athletes developed de-novo ECG changes following COVID-19 infection, of which 88% revealed inflammatory cardiac sequelae. Whereas most athletes in question reported cardiac symptoms and would have been assessed as standard of care, a small minority were asymptomatic. In the absence of cardiac symptoms de-novo ECG changes post COVID infection contributed to 20% of all cases of cardiac inflammation.

References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet (British edition)*. 2020;395(10223):497-506. doi:10.1016/s0140-6736(20)30183-5
2. Chung MK, Zidar DA, Bristow MR, et al. COVID-19 and Cardiovascular Disease: From Bench to Bedside. *Circ Res*. 2021;128(8):1214-1236. doi:10.1161/CIRCRESAHA.121.317997
3. Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm*. 2020;17(9):1463-1471. doi:10.1016/j.hrthm.2020.05.001
4. Finocchiaro G, Papadakis M, Robertus JL, et al. Etiology of sudden death in sports: insights from a United Kingdom regional registry. *J Am Coll Cardiol*. 2016;67(18):2108-2115. doi:10.1016/j.jacc.2016.02.062
5. Pelliccia A, Solberg EE, Papadakis M, et al. Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis: position statement of the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC). Published online 2019. doi:10.1093/eurheartj/ehy730
6. Eichhorn C, Bière L, Schnell F, et al. Myocarditis in Athletes Is a Challenge: Diagnosis, Risk Stratification, and Uncertainties. *JACC Cardiovasc Imaging*. Published online 2020. doi:10.1016/j.jcmg.2019.01.039
7. Moulson N, Petek BJ, Drezner JA, et al. SARS-CoV-2 Cardiac Involvement in Young Competitive Athletes. *Circulation*. Published online April 17, 2021. doi:10.1161/CIRCULATIONAHA.121.054824
8. Martinez MW, Tucker AM, Bloom OJ, 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*. Published online March 4, 2021. doi:10.1001/jamacardio.2021.0565
9. Phelan D, Kim JH, Chung EH. A Game Plan for the Resumption of Sport and Exercise after Coronavirus Disease 2019 (COVID-19) Infection. *JAMA Cardiol*. Published online 2020. doi:10.1001/jamacardio.2020.2136
10. Bhatia RT, Marwaha S, Malhotra A, 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(12):1242-1251. doi:10.1177/2047487320930596

11. Phelan D, Kim JH, Elliott MD, et al. Screening of Potential Cardiac Involvement in Competitive Athletes Recovering from COVID-19: An Expert Consensus Statement. *JACC Cardiovasc Imaging*. Published online 2020. doi:10.1016/j.jcmg.2020.10.005

12. Kim JH, Levine BD, Phelan D, et al. Coronavirus Disease 2019 and the Athletic Heart: Emerging Perspectives on Pathology, Risks, and Return to Play. *JAMA Cardiol*. Published online 2020. doi:10.1001/jamacardio.2020.5890

13. McKinney J, Connelly KA, Dorian P, Fournier A, Goodman JM, Grubic N, Isserow S, Moulson N, Philippon F, Pipe A, Poirier P, Taylor T, Thornton J, Wilkinson M JA. COVID-19 - Myocarditis and Return-to-play: Reflections and Recommendations from a CanadianWorking Group,. *Canadian Journal of Cardiology*. Published online 2020. doi:https://doi.org/10.1016/j.cjca.2020.11.007

14. Castelletti S, Gervasi S, Ballardini E, et al. The Athlete after COVID-19 infection: what the scientific evidence? What to do? *Panminerva Med*. Published online September 30, 2022. doi:10.23736/S0031-0808.22.04723-1

15. D'Ascenzi F, Castelletti S, Adami PE, 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;29(16):2120-2124. doi:10.1093/eurjpc/zwac180

16. Sharma S, Drezner JA, Baggish A, et al. International Recommendations for Electrocardiographic Interpretation in Athletes. *J Am Coll Cardiol*. 2017;69(8):1057-1075. doi:10.1016/j.jacc.2017.01.015

17. Kligfield P, Gettes LS, Bailey JJ, et al. Recommendations for the Standardization and Interpretation of the Electrocardiogram. *Circulation*. 2007;115(10):1306-1324. doi:10.1161/CIRCULATIONAHA.106.180200

18. Oxborough D, Augustine D, Gati S, et al. A guideline update for the practice of echocardiography in the cardiac screening of sports participants: a joint policy statement from the British Society of Echocardiography and Cardiac Risk in the Young. *Echo Res Pract*. 2018;5(1):G1-G10. doi:10.1530/ERP-17-0075

19. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation. *J Am Coll Cardiol*. 2018;72(24). doi:10.1016/j.jacc.2018.09.072

20. Buttà C, Zappia L, Laterra G, Roberto M. Diagnostic and prognostic role of electrocardiogram in acute myocarditis: A comprehensive review. *Annals of Noninvasive Electrocardiology*. 2020;25(3). doi:10.1111/anec.12726

21. Morgera T, di Lenarda A, Dreas L, et al. Electrocardiography of myocarditis revisited: Clinical and prognostic significance of electrocardiographic changes. *Am Heart J*. Published online 1992. doi:10.1016/0002-8703(92)90613-Z

22. Akritidis N, Mastora M, Baxevanos G, Dimos G, Pappas G. Electrocardiographic Abnormalities in Patients With Novel H1N1 Influenza Virus Infection. *Am J Cardiol*. 2010;106(10):1517-1519. doi:10.1016/j.amjcard.2010.06.078

23. Lampert J, Miller M, Halperin JL, et al. Prognostic Value of Electrocardiographic QRS Diminution in Patients Hospitalized With COVID-19 or Influenza. *Am J Cardiol*. 2021;159:129-137. doi:10.1016/j.amjcard.2021.07.048

24.   Elias P, Poterucha TJ, Jain SS, et al. The Prognostic Value of Electrocardiogram at Presentation to Emergency Department in Patients With COVID-19. *Mayo Clin Proc.* 2020;95(10):2099-2109. doi:10.1016/j.mayocp.2020.07.028

25.   Mahrholdt H, Wagner A, Deluigi CC, et al. Presentation, Patterns of Myocardial Damage, and Clinical Course of Viral Myocarditis. *Circulation.* 2006;114(15):1581-1590. doi:10.1161/CIRCULATIONAHA.105.606509

26.   Tahir E, Starekova J, Muellerleile K, et al. Myocardial Fibrosis in Competitive Triathletes Detected by Contrast-Enhanced CMR Correlates With Exercise-Induced Hypertension and Competition History. *JACC Cardiovasc Imaging.* 2018;11(9):1260-1270. doi:10.1016/j.jcmg.2017.09.016

27.   Baggish AL. Focal Fibrosis in the Endurance Athlete's Heart. *JACC Cardiovasc Imaging.* 2018;11(9):1271-1273. doi:10.1016/j.jcmg.2017.09.015

28.   Gluckman TJ, Bhave NM, Allen LA, et al. 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play. *J Am Coll Cardiol.* Published online March 2022. doi:10.1016/j.jacc.2022.02.003

29.   Harris KM, Mackey-Bojack S, Bennett M, Nwaudo D, Duncanson E, Maron BJ. Sudden Unexpected Death Due to Myocarditis in Young People, Including Athletes. *Am J Cardiol.* 2021;143:131-134. doi:10.1016/j.amjcard.2020.12.028

30.   Petek BJ, Moulson N, Baggish AL, et al. Electrocardiographic findings in young competitive athletes during acute SARS-CoV-2 infection. *J Electrocardiol.* 2022;72:13-15. doi:10.1016/j.jelectrocard.2022.02.005

Supplementary File Table 1: Clinical characteristics of COVID-19 positive (PCR) athletes with de-novo ECG patterns diagnosed with inflammatory cardiac sequelae

Table 1: Comparison of CMR data between athletes demonstrating de-novo ECG patterns and athletes undergoing a mandatory CMR.

Values are expressed as median (IQR); *P value <0.05 deemed statistically significant BSA: body surface area; CMR: cardiac magnetic resonance; ECG: electrocardiogram; LVEF: left ventricular ejection fraction; LVMWT: left ventricle maximal wall thickness; PCR: polymerase chain reaction; RVEF: right ventricular ejection fraction.

Table 2 Summary of cardiovascular symptom burden, de-novo ECG changes and MRI findings in overall cohort. CMRI: cardiovascular magnetic resonance imaging; CV: cardiovascular; ECG: electrocardiogram; IQR: interquartile range. *The clinical assessment as a minimum included a comprehensive history, systems review, examination, and electrocardiogram. Further onward investigations were performed based on the respective sports cardiologists, club or team doctor policy.

Figure 1: Challenges in establishing a diagnosis of myocarditis in athletes following COVID-19 infection. CMR: cardiovascular magnetic resonance; ECG: electrocardiogram; TTE: transthoracic echocardiogram; LV: left ventricle; RV: right ventricle.

Figure 2: Prevalence and diagnostic significance of de-novo 12-lead ECG changes after COVID-19 infection: study overview. ECG: electrocardiogram; TWI: T wave inversion.

Figure 3: Athlete case number 2. 20-day history of cardiovascular symptoms post COVID-19 infection. In comparison to his pre COVID-19 ECG (panel A), new T-wave inversion was observed in leads II, III, aVF, V3-V6 (panel B); a cardiac MRI (panel C) demonstrated mid-wall late gadolinium enhancement (LGE) in the basal inferior & inferolateral wall; subepicardial LGE in the mid lateral, apical lateral & inferior walls; with resolution of ECG changes 93 days post positive PCR (panel D).

Figure 4: Athlete case number 3. 28-day history of symptoms post COVID-19 infection. In comparison to his pre COVID-19 ECG (panel A), a reduction in T-wave amplitude II, aVF; biphasic T III was observed post COVID-19 infection (panel B). A cardiac MRI (panel C) a pericardial effusion around the basal inferior wall with ↑signal on T2-STIR images; an abnormal T1 signal in the mid inferolateral wall; and subepicardial LGE in the basal and mid inferolateral wall. Resolution of ECG changes observed 170 days post positive PCR (Panel D).