INFECTIOUS DISEASES AND THE RISK OF MYOCARDITIS

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INTRODUCTION – INFECTIONS AND THE HEART

In all higher organisms the heart is the most conserved and protected organ in evolutionary but also ontogenetic terms. This is because its function is essential for life and despite interspecies differences, common robust developmental pathways exist in all species[1]. These conserved pathways led not only to similar developmental patterns but also to a powerful organ-specific immune system illustrated by the hearts resilience to potentially devastating diseases such as cancer[2] and infections. The cardiac immune system is of such importance, that cardiac resident immune cells and pathways not only protect against infection or neoplasia, but contribute significantly to homeostasis and even cardiac remodeling and recovery from ischaemia[3]. These processes, however, are so complex that until now they are difficult to emulate in a therapeutic approach[4]. Immune cells also play a significant role in the beneficial effects of exercise on the heart, where exercise triggered immune-modulations are cardioprotective[5] making the immune system a central part of protection, metabolism and homeostasis in the heart. The consequence of such a robust natural defense system is the comparatively low incidence of infections involving cardiac tissues. Interestingly, subclinical inflammatory cardio-vascular processes are increasingly recognized as a driver for chronic ischaemic and atherosclerotic heart disease[6].

Although one of the most common reasons of cardiac events in sports (of up to 20%)[7] and important cardiac reason to stop sports participation, myocarditis is difficult to diagnose; for sports physicians and sports cardiologists alike. It is therefore important for the sports physician or team doctor to be familiar with the diagnosis and management of myocarditis. Important, as the contemporary approach in myocarditis diagnosis (now multimodal and multi-disciplinary), and management (now much less conservative and more individualized) is quite different from before.

AETIOLOGY OF MYOCARDITIS

The recent discoveries of disease modulating cardiac inflammatory processes have also altered the view and classification of infectious or inflammatory diseases of the heart[8]. Previously, myocarditis and pericarditis were described as different and non-related entities, while disease diagnosis and treatment focused largely on an infective aetiology. The new ESC myocarditis and pericarditis guidelines now recognise other important causes (besides viruses, bacteria or parasites) such as auto- inflammatory and immune diseases, genetics, drugs but also cancer. A new terminology, incorporating these new paradigms coined the term inflammatory myopericardial syndrome (IMPS)[8]. Nevertheless, myocarditis—the focus of this review—remains distinct from an isolated pericardium inflammation.

The more comprehensive approach on myocardial inflammation also changes data on prevalence, which is likely to be underreported. Overall, incidence and prevalence of myocarditis depend on age and gender, with the younger and male population more affected. The global prevalence (using data from an albeit limited age range between 35-39 years) is estimated to be between 4.2 – 8.7 per 100000[9]. These data are however highly dependent on diagnostic criteria and tools used. The inclusion of cardiac MRI in the diagnostic pathway, for example, significantly increases the diagnostic yield while the inclusion of non-infective aetiology further

Table 1

Presentation	*Signs and symptoms*	*Target diagnostic tests*	*Management*
Cardiac dysfunction	*Chest pain, SOB, fatigue, decreased performance, dizziness, peripheral oedema (rare)*	*12-lead ECG, Echocardiogram, CMR, biomarkers (hs Troponin, aBNP)*	*Rest, abstinence from exercise, pharmacological agents (ACE inhibitors, ARBs, Beta Blockers and others)*
Arrhythmias	*Palpitations, dizziness, syncope, chest pain*	*12-lead ECG, ambulatory 24h ECG, stress ECG, CMR*	*Rest, abstinence from exercise, pharmacological agents (beta blockers and others)*
Systemic inflammation (shock)	*Fever, malaise, fatigue, cardiovascular compromise*	*Biomarkers (CRP, ESR, FBC, specific antibodies and cytokines)*	*Antibiotics, antiviral, anti-inflammatory drugs (Aspirin, NSAIDs, corticosteroids)*

Table 1: Summary of most common disease presentations in the athlete setting with associated symptoms, the required diagnostic tests and management options. ARB=angiotensin receptor blocker; ACE=angiotensin converting enzyme; CMR=cardiac magnetic resonance; ECG=electrocardiogram, hs Troponin=high sensitivity troponin, NSAID=non-steroidal anti-inflammatory drugs.

changes such estimates[10]. Taking the new definition of IMPS into account (including non-infective causes), the clinical prevalence of the entity described as myocarditis is with certainty higher then quoted above. On the other hand, data on severity of myocarditis, overall resolution of symptoms and sequalae cited in the athlete literature are not athlete-specific and should be interpreted with caution as figures on associated ventricular dysfunction or incomplete resolution are certainly overestimated[11].

This is of particular importance to the sports physician and sports cardiologist, as myocarditis presenting in athletes is often mild and subtle. If missed, however, myocarditis could have significant long term consequences for health and sports participation. The diagnosis should be guided by clinical signs and symptoms, whether a proven infective pathology is present or not. Therefore, to avoid missing cases, a diagnosis of myocarditis in sports medicine practice should not rely on confirmed infective aetiology, but should be based on the spectrum of clinical presentation and positive findings on recommended diagnostic tests[8]. The sports participation and short and long term athlete health consequences of myocarditis are indeed not so much dependent on aetiology but more on the effect on cardiac structure and function.

It remains true, nevertheless, that viral infections are often the cause and trigger that lead to either direct damage to cardiac structure or cause a pathological inflammatory and immune response. Enterovirus, SARS-CoV-2, adenovirus, parvovirus B 19, Ebstein-Barr Virus, human herpes virus, and certain influenza virus strains are commonly associated with myocarditis, either as direct causative pathogens or as triggers for a damaging immune response[12]. The high number of SARS-CoV-2 infections and the high virulence in the immune compromised and elderly population, predictably led to an increase in the incidence of myocarditis during the Covid Pandemic. The incidence of SARS-CoV-2-associated myocarditis is reported to be ten-fold higher that of non-SARS-CoV-2 myocarditis[13]. Despite this, data on the incidence in athletes is extremely heterogenous.

PRESENTATION OF MYOCARDITIS

As myocarditis presents in many ways, clinical acumen and alertness are key to allow clinicians to recognize the disease's subtle signs.. The well-known variety of presentations, signs and symptoms led to an innovative, newly-proposed classification by the ACC expert consensus group; they propose four categories based on severity of disease, from subclinical myocarditis to disease requiring intensive care admission – the latter occurring much less frequently in athletes[14].

While the diagnosis of myocarditis rests on a variety of hospital-based diagnostic tests (Table 1), an almost detective-level of interrogation for mild signs and symptoms is paramount in making the diagnosis. Sports physicians are usually the first point of contact for an athlete with possible myocarditis. The most common scenarios with corresponding symptoms or signs are presented in Table 1. The most common presentation of an athlete with possible myocarditis include one or more of the following: new symptoms of palpitations, chest pain, shortness of breath, pre syncope or syncope. Importantly, symptoms related to a sudden and unexplained loss of athletic performance, such as fatigue, lack of stamina, reduction in peak performance, malaise and dizziness during exercise are important hallmarks of the disease. Often, but not always, a recent history of a rhinitis illness or infection are present. The commonly used 'diagnostic' suggestion that inflammatory and infective disease beyond mild nasal symptoms should raise higher suspicion (symptoms "below the neck" with systemic signs or symptoms such as fever and malaise and muscle aches) holds true, as it is extremely rare for a common mild cold to cause myocarditis. However, as described above, myocardial involvement can happen even in mild infections and a high rate of suspicion is required, while at the same time understanding that myocarditis is a rare event in athletes.

Of Importance in paediatric and adolescent patients is the so called multi-inflammatory syndrome (MIS). Myocarditis could be part of a spectrum of inflammations in other organ systems. This is usually the case in more severe presentations, where careful evaluation of all organ systems is

paramount[15] – unlikely to be found in young athletes investigated in the outpatient setting (Table 1).

DIAGNOSTIC APPROACH

Once the decision is made to investigate an athlete for the presence of myocarditis, a referral to a sports cardiologist is indicated, in particular as single cardiac screening tests performed in the club setting (such as a 12-lead ECG), have low sensitivity and changes are often unspecific. New repolarization changes, such as T-wave inversion or ST elevation or suppression, new atrial or ventricular ectopics and arrhythmias, but also new left bundle branch block or heart blocks should raise suspicion and prompt a full diagnostic work up[16,17] (see Figure 1).

Blood biomarkers for evidence of a general (CRP, ESR) or myocardial (hsTroponin) inflammatory process should be taken. False positive Troponin levels secondary to exercise participation within the last 48h are a frequent confounder, repeat tests after resting periods improve sensitivity[18].

IMAGING

Imaging, to detect cardiac dysfunction or more subtle signs of myocardial inflammation, such as focal wall motion abnormalities, the presence of oedema, and post inflammatory processes such as fibrosis should then always be conducted. The first line imaging tool remains echocardiography, where global cardiac dysfunction or wall motion abnormalities can be detected. Modern speckle tracking echocardiography has a good sensitivity for detecting also focal cardiac dysfunction and correlates moderately well to cardiac MRI findings such as fibrosis[19]. Echocardiography alone however has a low sensitivity, as active inflammation, oedema or fibrosis cannot be visualized. Therefore, cardiac MRI is the gold standard imaging tool and should always be performed if suspicion is high or first line tests (ECG, Echocardiogram, biomarkers) yield abnormal or borderline findings. Modern cardiac MRI techniques if used in a multiparametric approach including inflammation (T1), oedema (T2) and fibrosis (Gad enhancement) imaging can reliably detect subtle changes of myocarditis[20] (see Figures 2 and 3).

Other secondary imaging techniques could facilitate the diagnostic work up. These include computed tomography (for

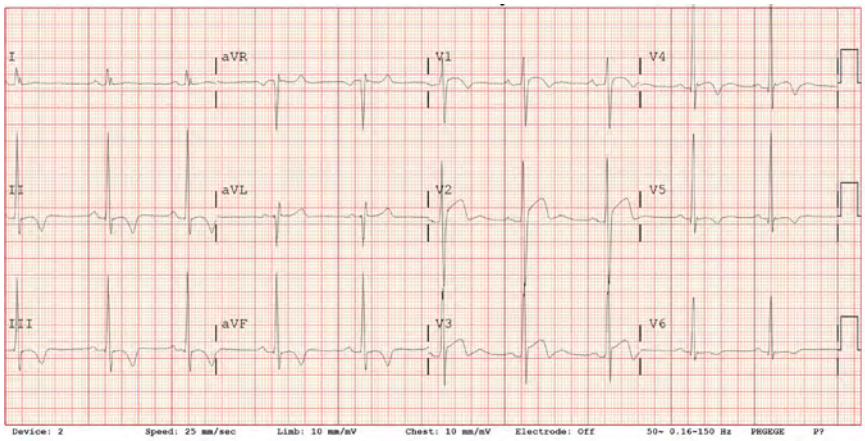


Figure 1: 12-lead ECG showing repolarisation changes such as widespread ST changes with ST elevation in leads V2-V4 and T wave inversion in leads II, aVF, V4-6. T wave inversion in lead III, but also the ST elevation with early repolarisation can be found in healthy athletes making a differential diagnosis challenging. Comparison ECGs before and during/ after infection can be helpful when available.

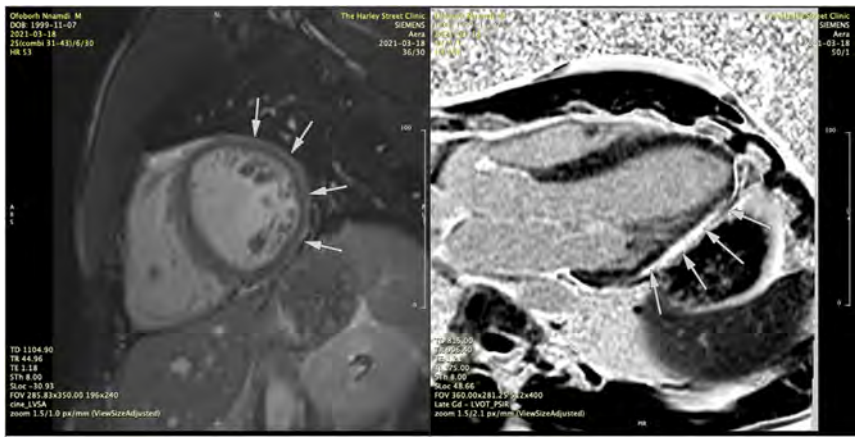
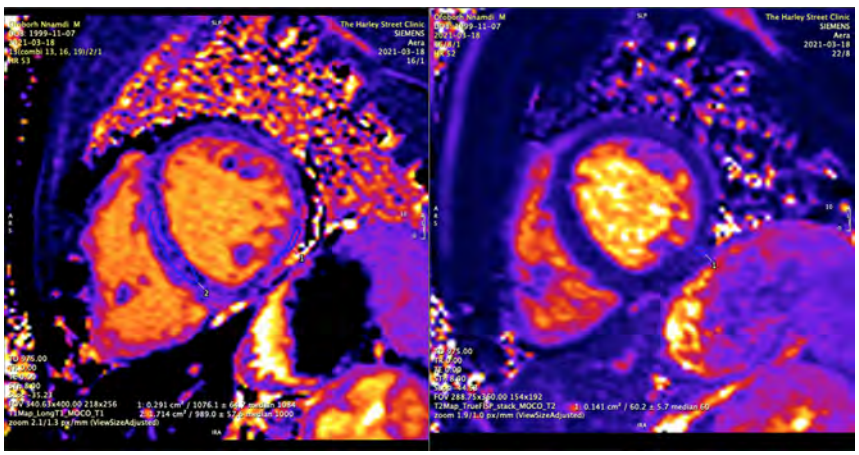


Figure 2: Cardiac MRI images after late Gadolinium contrast enhancement affecting the LV epicardial layers in short axis (left) and long axis (right). Arrows indicate areas of enhancement indicating fibrosis.



Native myocardial T1 mapping (989 at the level of the mid-interventricular septum; 1076 ms in the mid lateral wall; normal 890-1050 ms)

Pre-contrast myocardial T2 mapping (60 ms; normal <50 ms)

Figure 3: Native myocardial T1 mapping showing increased T1 times in the mid lateral LV myocardial wall as an abnormality indicating possible inflammatory process/oedema (left). Increased T2 mapping times indicating LV epicardial inflammation/oedema corresponding to the LV areas affected by fibrosis (right).

the further characterisation of anatomy and exclusion of pericardial and associated lung involvement) and positron emission tomography (for a detailed characterisation of the inflammatory process); but they remain reserved for specific clinical scenarios[12].

ARRHYTHMIA DETECTION

The myocardial inflammation cascade with release of homeostasis-changing substances, oedema and post inflammatory fibrosis, is a substantial risk substrate for arrhythmias. Cardiac MRI – sensitive to these changes – is therefore an essential tool in the diagnostic work up of myocarditis[20]. However, even if these changes are not present, arrhythmia detection is a mandatory key component of the diagnostic pathway.

While the 12-lead resting ECG remains the primary test in the myocarditis work up, its sensitivity in clinical but in particular subclinical myocarditis is low. Serial ECGs (comparing pre and post infection ECG) increase ECG sensitivity for myocarditis [21]. Nevertheless, a myocarditis work up should not stop here, but include longer term ambulatory rhythm monitoring in particular during exercise. A 24h ambulatory ECG including during exercise (Figure 4) and exercise stress ECG (Figure 5) should therefore always be part of the diagnostic pathway[8,11]. As subtle signs and symptoms of myocarditis are often detected during exercise and often represent manifestations of new arrhythmias, exercise rhythm assessment is important. In particular ventricular ectopic beats or non-sustained ventricular tachycardias are hallmarks of an otherwise subclinical disease process (Figure 4 and 5).

MANAGEMENT OF MYOCARDITIS IN THE SPORTS SETTING

In suspected myocarditis, early involvement of a sports cardiologist is advised. When the diagnosis is confirmed, a multi-disciplinary team approach is required to expertly interpret and manage diagnostic findings[14]. Management is informed by the latest consensus papers and guidelines[8,11,14], but most importantly should be based on the disease presentation and history, diagnostic findings and risk factors of the individual athlete. This holds true for acute disease management, medical therapy, and, important for athletes, the return to play pathway.

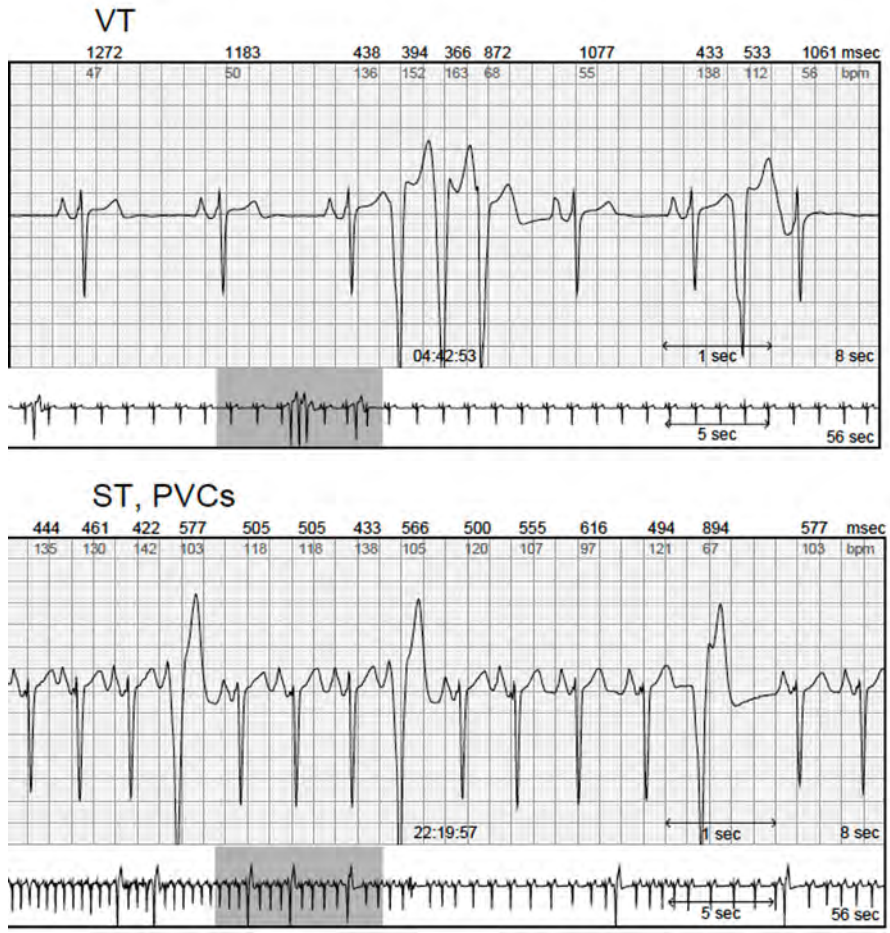


Figure 4: 24h ECG monitoring showing several episodes of ventricular ectopics including triplets (top) and as shown here multiple monomorphic, but overall polymorphic, ventricular ectopics (bottom) at exercise HRs with an abnormal ectopic burden of 5 % of recording.

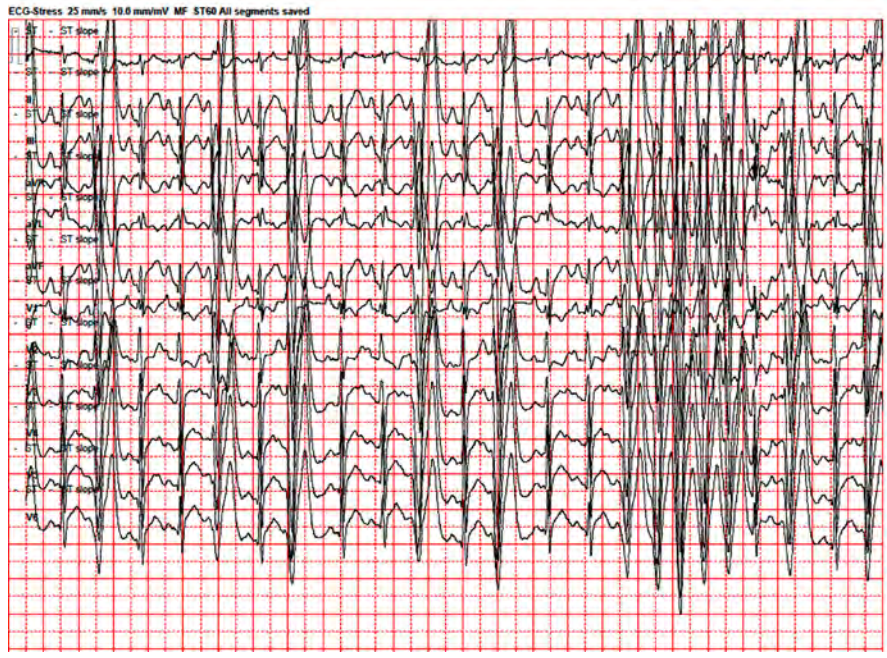


Figure 5: Exercise stress ECG on treadmill during exercise showing normal sinus tachycardia at 150 bpm with intermittent single ventricular ectopics progressing to an episode of non-sustained monomorphic ventricular tachycardia at approx. 220 bpm. Spontaneous reversal into sinus rhythm, the athlete did not report symptoms.

Acute management aims to stabilize the myocardial inflammatory and (auto-) immune process as the main culprit for sequelae as described above. This includes medical therapy and avoiding strenuous exercise including competitive sports. Drug therapy, aimed at controlling the inflammatory process, include NSAIDs, Aspirin, cortico-steroids (in more severe cases), and Colchicine (with pericardial involvement)[14]. The evidence base for treating out of hospital myocarditis with Aspirin is based on an understanding of the pathophysiological mechanisms. Comprehensive data on its effect are lacking. It can however be considered as it is the acute inflammatory stage of the disease that is crucial in the prevention of significant sequelae such as arrhythmias and cardiac dysfunction.

We are far from a targeted causative treatment approach to safely avoid these medium and long term changes. Arrhythmias should be treated based on their type. Ventricular ectopics and tachycardia in the athlete are most often treated with betablockers, ventricular dysfunction and heart failure treatment should follow current practice and guidelines. The short term use of ACE inhibitors or ARBs in mild cardiac dysfunction or even with normal cardiac function should be considered, as these drugs act on the profibrotic pathways and classic animal studies have shown a reduction in fibrosis in myocarditis[22], large scale clinical data specific to myocarditis on its benefit are however incomplete. Longitudinal surveillance on disease progression should rely on above diagnostic tests and focus on findings and symptoms of the individual case. Biomarkers such as hs Troponin, if credibly elevated at the first assessment, should be repeated within the first month, a full assessment including ECG, Echocardiogram and rhythm monitoring as well as a repeat cardiac MRI should be done 4-8 weeks after the initial assessment.

RETURN TO PLAY

As with management of the disease, timing of return to training and play varies considerably depending on severity, stage of presentation and present risk factors and should be mostly informed by signs, symptoms and diagnostic findings of the individual case.

In general, current guidelines and consensus papers advocate for a return to play after three to six months[8,11,14]. However, a case by case assessment and risk stratification strategy often allows a return to exercise, training and competition in a shorter time frame. This novel concept rests on an approach informed by regular repeat assessments and identification of clinically relevant risk factors, such as arrhythmias, continuing inflammation or signs of cardiac dysfunction. It is more meaningful to determine the time point of resuming athletic training by the stage of the inflammatory process. If asymptomatic, with normal hs Troponin, echocardiogram and cardiac MRI and the absence of arrhythmias, training can often resume after one to two months. Even after return to competitive sports, athletes should be reassessed every 3 to 6 months in the first year, earlier, if new symptoms occur.

PROTECTION AND PREVENTION FROM MYOCARDIAL INVOLVEMENT OF INFECTIONS

Infection prevention in the athlete is paramount as described in this journal edition and is the best preventive measure also for myocarditis. Risk factors for infections such as sleep deprivation, immune system deficiencies but also overtraining and fatigue can lower the barriers for myocardial involvement in any infection. In general, vaccinations as highlighted in this edition can prevent infection and therefore myocarditis, but there is no direct evidence for the rationale of vaccination as a targeted prevention strategy for myocarditis beyond the general protection form the infectious disease in question.

Vaccine associated myocarditis has been described for the small pox and SARS-CoV-2 mRNA vaccinations[14]. The myocardial and cardiac immune response to the SARS-CoV-2 mRNA vaccination has not been conclusively investigated and described, but SARS-CoV-2 mRNA vaccination associated myocarditis during the pandemic occurred but was indeed rare. Data from the US military and the UK Health Security Agency (HSA) show comparable incidence. A US military registry reported 23 cases of myocarditis in 2.8 million vaccine doses given[23], similar to the 10 myocarditis reports per million doses given in the UK. Of practical importance, guidance released by the UK HSA did not recommend an increased abstinence from competitive sports after SARS-CoV-2 mRNA vaccination *(https://www.gov.uk/government/publications/myocarditis-and-pericarditis-after-covid-19-vaccination/myocarditis-and-pericarditis-after-covid-19-vaccination-guidance-for-healthcare-professionals#background)*.

CASE: MYOCARDITIS IN AN ELITE FOOTBALLER

Presentation: Team doctor referral to the sports cardiology clinic, self-reported new

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onset of mild symptoms of very occasional light headedness and shortness of breath for 2 months during training or games after high intensity efforts, such as sprinting or fast running with the ball. Frequency of symptoms now increasing, affecting his performance. No chest pain, pre syncope or syncope, no family history of inherited cardiac disease, no cardiac medication history. Possible mild coryzal infection 3 months ago, no virology performed.

Examination: No evidence of cardiac compromise, normal heart sounds, no heart murmur, good volume regular pulses with very occasional ectopics at rest. Bilateral air entry, no dyspnoea. No evidence of an infectious or inflammatory process.

Biomarkers: Elevated hsTroponin above normal range on repeated tests, normal ESR and CRP.

Echocardiogram: Structurally and functionally normal heart without dyskinesia or wall motion abnormalities. No pericardial effusion.

Cardiac MRI: Mildly dilated LV with low normal global systolic function (LVEF 54%), often seen in healthy athletes, but mild hypokinesia of the mid lateral LV wall. Mildly dilated RV with normal global systolic function (RVEF 51%). Extensive epicardial late gadolinium enhancement involving the entire mid lateral and inferior and apical lateral and inferior LV wall and the basal lateral wall. T2 mapping and T2w STIR imaging, evidence of a degree of residual LV epicardial inflammation/oedema in correspondence with the LV segments positive to late enhancement. No pericardial thickening or pericardial effusion. Changes are typical for sub-acute myocarditis. A pattern of T1, T2 and LGE abnormalities indicate presence of myocardial oedema and possible epicardial and myocardial necrosis.

Diagnosis: Likely subacute myocarditis with normal cardiac function but structural changes of post inflammatory fibrosis of the LV and non-sustained ventricular tachycardia.

Management: Avoid exercise and competitive sports until review; low intensity activities such as walking, slow cycling allowed. Beta blocker treatment to manage frequent ventricular ectopics and non-sustained VT commenced. ACE inhibitor started to prevent further fibrosis and support the low normal LV function. Hs troponin elevated as evidence of an ongoing inflammatory process hence Aspirin started until review. Repeat ECG and echocardiogram after 4 weeks showed no new findings. Exercise test 4 weeks after betablocker treatment start, but off betablocker 3 days before testing, continued to show ventricular ectopics and short runs of non-sustained VT. Cardiac MRI at 6 weeks showed no increase in fibrosis and some regression of oedema. After 3 months no evidence of an active inflammatory process with normalized hs Troponin and other biomarkers, cardiac MRI with same fibrosis pattern and extent, no oedema. Athlete without symptoms at rest. Exercise ECG after 3 months on betablocker treatment showed ventricular ectopics but no ventricular tachycardia. ACE inhibitor and Aspirin were discontinued. In a shared decision making process between athlete, sports cardiologist, team doctor, and athlete's family it was decided to resume staged exercise and training on betablocker treatment and continuing 3 monthly sports cardiology follow up. Athlete could return to professional football after 7 months without further significant symptoms or events, but despite betablocker treatment remains at a higher risk than healthy athletes for ventricular arrhythmias and cardiac events. 6 monthly sports cardiology follow up and close collaboration with team sports physician continues.

KEY TAKE HOME MESSAGES - MYOCARDITIS

1. *Presentation is highly variable*
2. *Aetiology includes direct exposure to viral pathogens but their presence is not necessary, alternative aetiologies are underreported*
3. *Thorough clinical assessment of signs and symptoms is key for diagnosis*
4. *Diagnostic work up should be informed by the specifics of each individual case and should include CMR imaging and ambulatory rhythm assessment during exercise*
5. *Abstinence from exercise in the acute phase must be observed*
6. *Repeat assessment should happen after acute phase – in the window of 4-8 weeks after presentation including CMR and ambulatory rhythm monitoring during exercise*
7. *Exercise restriction should be individualized and return to exercise can start before 3 months if no risk factors and symptoms are present*
8. *Risk factors include myocardial scars (fibrosis), arrhythmias, especially during exercise, continuing inflammation (biomarkers) and cardiac dysfunction (Echo, CMR)*
9. *Return to exercise on pharmacological treatment is permissible*
10. *Shared decision making for RTP is key*
11. *A multi-disciplinary approach to management is best clinical practice*

References
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