Return to sport: First data from the Nationwide German Myocarditis Registry for athletes

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There is currently no evidence how to treat athletes with suspected or proven myocarditis in the context of “return to sport” (RTS). Addressing this issue, a multi-centre, web-based online registry was initiated in 2011 to record athletes presenting with suspected or proven myocarditis. Our nationwide registry is the first successfully implemented database of competitive athletes with suspected or proven myocarditis. Besides baseline data, available clinical data and the physician’s recommendation in terms of sport participation were recorded. A telephone interview for clinical follow-up was performed one year (1FU) after the initial presentation. 98 athletes (77 males, mean age 30.9 years) were analysed. Data from 1FU were available for 74 athletes. At baseline, 72% of the athletes reported infection-associated symptoms prior to the first medical contact. A high percentage of athletes present abnormal clinical or technical cardiac findings. Abnormal rest-ECG was seen in 41/74 athletes, abnormal echo in 37/74, abnormal MRI in 32/74. During the period prior to 1FU, there were no incidences of sudden death or cardiac arrest. Most athletes return to sport within one year, however duration and intensity of training were still reduced in one third of the athletes. A total of 58/74 were fully reintegrated in sport, 10/74 partially, and 5/74 were not able to participate in sport. Greater age was delineated as the only significant predictor for incomplete reintegration after one year. Consequently, even if there is missing evidence regarding how to treat athletes with suspected myocarditis in context of RTS, the chosen approach in terms of diagnostic work-up and decision regarding RTS seems to be safe. In summary, treating athletes with suspected or proven myocarditis continues to be challenging but register data will help to get a more precise idea how to treat athletes with myocarditis.

KEYWORDS
athlete, myocarditis, registry, return to sport, sports

1 | INTRODUCTION

1.1 | Background

Myocarditis is responsible for approximately 8% of sudden cardiac deaths in U. S. American college athletes. The real incidence of myocarditis is widely unclear and therefore estimative. Viral infections that also involve the myocardium are presumed to occur more frequently. Within the nationwide registry for sudden cardiac death in Germany, Bohm et al show sport-related sudden deaths by proven myocarditis in about 24% of athletes ≤35 years.
1.2 | Eligibility for RTS

There is no evidence supporting recommendations for how to treat athletes with suspected acute or chronic myocarditis in the context of RTS. For example, it is unclear when athletes should start with moderate exercise or which extent of diagnostics is necessary for physicians to make a positive decision regarding “return to training/return to competition.” This is especially true in cases with mild symptoms and an unremarkable follow-up, or in athletes with suspected involvement of the myocardium in the context of uncomplicated infections (e.g., infections of the upper respiratory tract). Recommendations proposed by the European Society of Cardiology (ESC), the American Heart Association (AHA)/American College of Cardiology, or the 36th Bethesda Conference (2005) can only be understood as helpful orientation for guiding clinical processes.4-6 In context of acute myocarditis, the point of RTS becomes most important. Studies with acutely infected mice participating in swimming exercise presented a total mortality of about 50%.7,8 Vigorous activity enhances viral replication and results in higher structural tissue damage.7,9 Lethality decreased significantly when exercise was started just 8 days after acute infection of the animals.

In consideration of possible severe consequences of an underestimated or incorrectly estimated myocarditis, decisions for “return to training” or “return to competition” are predominately conservative. This leads to months of training failure and missing competitions, which is a considerable issue for professional athletes. On the other hand, the volume of diagnostic methods varies strongly for these commonly chosen conservative procedures, particularly with regard to mild clinical cases.

1.3 | Aims of the myocarditis registry

The current recommendation of the AHA/ACC emphasizes “the need for additional research to refine risk stratification for sudden death after acute myocarditis.”4 The “Nationwide German Myocarditis Registry” addresses this issue by generating a prospective database, which in turn should allow more evidence-based recommendations in affected athletes. This registry aims to build prospective standardized documentation of current diagnostic procedures for suspected myocarditis in athletes. Based on the data, the following questions are addressed:

Which diagnostic and therapeutic measures are performed in athletes with (suspected) myocarditis? Which recommendations in terms of RTS were made? Which adverse events occur during follow-up? Are there any diagnostic or clinical parameters that predict outcome?

2 | MATERIALS AND METHODS

The web-based “Nationwide German Myocarditis Multicentre Registry” was initiated in 2011 after being approved by the local Institutional Review Board. Seventeen institutions are currently participating. Written informed consent was obtained from all subjects. Competitive athletes of both genders were recruited who presented with suspected or proven myocarditis and who participated in at least one competition per year within Olympic sports.

The diagnosis of proven or suspected myocarditis was assessed by the attending medical doctor. Athletes with existing structural cardiac diseases were excluded. Recruitment took place in the participating institutions from (a) athletes who were referred by a general practitioner or family doctor, or (b) during first medical contact in one of the participating institutions.

Besides baseline data (gender, age, competitive level, discipline), available clinical data (e.g., laboratory results, symptoms, technical results) and recommendations in terms of training and competitive sports participation were recorded. A follow-up telephone interview was performed 1 year after the initial presentation using a standardized questionnaire to explore duration of persisting symptoms, severe cardiac complications (e.g., heart failure, physical fitness and limitations, reintegration to sport), and possible pending further examinations. Additional follow-ups are planned after three and 5 years (Figure 1).

Statistical analyses were performed using the software program Excel and GraphPad. Categorical variables of the

FIGURE 1 Workflow “Nationwide German Myocarditis Multicentre Registry.” ECG, electrocardiogram; Echo, echocardiography; Lab, laboratory results; CMR, cardiac magnetic resonance imaging; EMB, endomyocardial biopsy
registry are presented in absolute numbers and as a percentage, while continuous variables are expressed as mean ± SD. For subgroup analyses, Fisher’s exact test and Student’s *t* test were used. *P* value below .05 was considered significant.

3 | RESULTS

3.1 | Athlete’s characteristics

Due to insufficient, missing, or implausible information, 22 (18.3%) cases had to be excluded from the analysis. Consequently, a total of 98 cases (77 males) were analyzed. Data from IFU were available for 74 cases (57 males). Information about the first medical contact in the context of myocarditis (“V1”) was available for 82 cases (65 males). Mean age of these athletes (*n* = 82) was 30.9 years at the time of inclusion into the registry. Most athletes participate in cycling, soccer, or athletics.

Most athletes had a training history of more than 5 years (73.9%). Recorded training frequency was predominately 4-6 times per week (49.3% at least four times), while training duration indicated a peak between 3-10 hours per week (42.9% at least 6 hours).

3.2 | Symptoms

The first medical contact (V1, *n* = 82) was mainly driven by clinical symptoms (for Visit 1 pectangina in 34.1%, reduced perceived fitness in 15.9%, graded as level 3 (1 = minor restriction, 4 = major restriction), palpitations in 13.4%, and dyspnea in 9.8%). There was information about previous infectious events in 72.0%, while 17.1% had no history of infection (missing data 11%). The most common site of infection was the upper respiratory tract (71.4%).

3.3 | Diagnostic work-up

Medical contacts show a range of athletes with only one visit (37.8%) or two visits (28.6%), up to a maximum of nine visits (1.7%). More than two visits were only reported for 33 athletes (33.7%). First medical contact in one of the participating institutes was documented in 59 cases and took place in an early stage of clinical treatment (40.7% of athletes at V2, 28.8% at V1). In most cases, the first medical contact occurred at the general practitioner (28.0%) or in an emergency room (24.4%). At V2, 46.7% were seen in one of the participating institutes.

ECG, laboratory testing, and echo were predominately performed at V1. A compilation of performed diagnostic examinations at first contact within an institute (Table 1) illustrates a higher number of performed ECG, echo, and stress tests compared to V1 in general. About all visits, EMB was performed in a total of 4 athletes (4.1%). All confirmed the diagnosis of myocarditis.

3.4 | Abnormal diagnostic findings

Table 2 shows the distribution of abnormal diagnostic findings. Interpreting laboratory results was difficult, because of particularly implausible data caused by different reference values. At V1, cardiac troponins were determined in 30 cases (36.6%) and showed elevated values (>0.04 ug/L) in 16 athletes (19.5%). Cardiac troponins were determined in 45 cases (45.9%) during clinical work-up and were elevated in 23 athletes (23.5%).

3.5 | Recommendation for sport participation

Restriction from sports was declared by the attending physician, for example, cardiologist (31.5%), general

### Table 1

Compilation of performed diagnostic examinations at V1, during all visits and at first contact within one of the participating institutes

| Examination                  | V1 (n = 82) | V1 (%) | All visits (n = 98) | All visits (%) | First visit at institute (n = 59) | First visit at institute (%) |
|------------------------------|-------------|--------|---------------------|----------------|---------------------------------|-----------------------------|
| ECG                          | 61          | 74.4   | 85                  | 86.7           | 50                              | 84.7                        |
| Laboratory                   | 52          | 63.4   | 58                  | 59.2           | 28                              | 47.5                        |
| Echocardiography             | 49          | 59.8   | 68                  | 69.4           | 43                              | 72.9                        |
| CMR                          | 31          | 32.8   | 48                  | 49.0           | 20                              | 33.9                        |
| Stress test                  | 17          | 20.7   | 56                  | 57.1           | 32                              | 54.2                        |
| 24 h-Holter ECG              | 20          | 24.4   | 36                  | 36.7           | 14                              | 23.7                        |
| EMB                          | 2           | 2.4    | 4                   | 4.1            | 0                               | 0                           |

*Note: Percentage value is due to all included cases at V1 (n = 82) rather or all included athletes for all visits (n = 98) and at first contact within participation institute (n = 59).*

*Abbreviations: CMR, cardiac magnetic resonance; ECG, electrocardiogram; EMB: endomyocardial biopsy.*
practitioner (20.4%), or a physician in the treating medical clinic (27.8%), at V1 either due to medical history, examination results, or technical results for 65.9% of the athletes. No restriction was declared in 18.3% (missing data in 15.9% of the athletes). Duration of sports restriction was subdivided into two peaks of incidence: for a duration of 1-4 weeks (37%), and for a duration of 3-6 months (26%).

Decision for training arrest was made in 70.0% by the first attending doctor and in 20.0% by the athletes themselves (10.0% missing data). Further, in most cases, physician recommendations resulted in a training interruption of 1-4 weeks (25.6%) or 1-3 months (10.98%). A training interruption of longer than 3 month was only performed in 10 cases (12.2%).

3.6  |  State of health at 1FU

A total of 46/74 (62%) athletes had their last medical consultation 10-12 months before the first follow-up interview. At 1FU, only 27.1% (n = 20) were scheduled for another visit due to myocarditis (eg, general practitioner, or cardiologist), and 16.2% still required medication to treat myocarditis. Further diagnostic examinations were planned for some athletes: laboratory retests (12.2%), further 24 h-Holter ECG (10.8%), stress tests (13.5%), and echo (10.8%). A total of 5.4% of the athletes were waiting for pending CMR, and no athlete was waiting for pending EMB. A total of 75.7% of athletes had no pending diagnostic examinations at 1FU (Figure 2).

After 1 year, 72% of the athletes stated an improved state of health (22% no change, 5% worsening). Most athletes (78.4%) were fully reintegrated in sport 1 year after inclusion into the registry, 6.8% were not able to practice their athletic discipline, and 13.5% were only partially reintegrated (Figure 3). Three of ten questions within the standardized questionnaire aimed at sport participation after 1 year, asking for the possibility to perform their discipline in general, as well changes in training intensity and duration compared to time before. Athletes were assigned to “partially reintegrated,” if one of the questions was answered with “reduced.”

There was a difference between males and females in RTS (fully reintegrated: males 82.5%, females 64.7%) and a less pronounced difference for “health status after 1 year” (health status evaluated as “improved”: males 73.7%, females 64.7%). Duration and intensity of training were reduced in 32.4% of the athletes. Persisting clinical disorders were predominantly reduced perceived fitness (12.2%), fatigue (8.1%), palpitations (6.8%), and dyspnea (5.4%). There were no cases of fainting or syncope.

3.7  |  Predictors for a worse outcome after 1FU

At 1FU, almost 72% of athletes reported at least partial relief of symptoms. However, 20.3% of all athletes were only partially reintegrated into sports activity. All athletes interviewed at 1FU were subdivided into two groups (Table 3):

1. Fully reintegrated to sport (“return,” n = 58).
2. Incompletely reintegrated in sport, that is, sport activity is still reduced or not possible (“no return,” n = 15).

One athlete had to be excluded, because of missing information.

Mean age of subgroup “no return” (39.59 years, SD 11.38) was significantly higher (unpaired t test, \( P < .0001 \), CI 95% of difference from 5.81-15.81) than the mean age of subgroup “return” (28.78 years, SD 7.85). There was no difference between the two groups in terms of initial conditions leading to first medical contact (infection and fever in this context, symptoms at V1), subsequent recommendation for “no sport,” or for several diagnostic results. There was a non-significant tendency with regard to gender differences (Fisher’s exact test: 0.0991), with completely reintegrated males in 83.9% vs females in 64.7%.

Supposing there will be a difference for RTS after 1 year between athletes with higher or lower training load, we analyze a subgroup 1 “high training load” (more than 6 hours training per week, n = 23) and a subgroup 2 “low training load” (0-6 hours training per week, n = 30). Limited by low number of available data at FU1, there was no significant difference between the groups for reintegration to sport (return to sport: 19/23 vs 24/30; Fisher’s exact test, \( P = 1.0000 \)) or training duration at follow-up compared to baseline (reduced training duration: 7/23 vs 10/30; Fisher’s exact test, \( P = 1.0000 \)).

Table 4 shows abnormal diagnostic results clustered for any abnormalities. Abnormalities found during diagnostics up to 1FU were seen in 64 of 74 athletes. However, the number of abnormal diagnostic results was not predictive for outcome in terms of RTS (Fisher’s exact test for \( \geq 2 \) abnormal clusters for subgroup “RTS” vs “limited or no RTS”: \( P = 1.0000 \); Fisher’s exact test for \( \geq 3 \) abnormal clusters for subgroup “RTS” vs “limited or no RTS”: \( P = 1.0000 \)).

4  |  DISCUSSION

According to the data of our nationwide myocarditis registry, athletes with suspected or proven myocarditis have a good prognosis in terms of RTS. Almost 72% of athletes reported at least partial relief of symptoms 1 year after...
inclusion into the registry, whereas only 20.3% were only partially reintegrated. Duration and intensity of training were still reduced in 32.4%. Reduced perceived fitness, fatigue, palpitations, and dyspnea were the leading clinical problems in athletes with persistent symptoms. Besides age, there is currently no parameter predictive for incomplete reintegration.

4.1 | RTS due to recommendation for sport participation

Due to a lacking database, existing recommendations are not evidence-based and reflect experts’ opinions.4-6 Athletes with suspected or definite myocarditis should be withdrawn from competitive sports for 3-6 months and undergo a reasonable period of convalescence of about 6 months following the onset of clinical manifestations.6 As the recommendations of the 36th Bethesda Conference suggest, returning to training and competition after a period of 6 months appears to be reasonable if left ventricular function, wall motion, and cardiac dimensions (based on echo) have returned to normal, clinically relevant arrhythmias are absent in Holter ECG monitoring, and exercise ECG, serum markers of inflammation and heart failure, as well as 12-lead-ECG have normalized.

As we see in our data, an initial recommendation for “no sport” was made in 65.9% of the athletes (mainly by the first attending doctor) with no difference between reintegrated and non-reintegrated athletes. Duration of sport prohibition showed two peaks: (a) a duration of 1-4 weeks (37%), possibly due to a soft symptomatic in the context of a suspected common cold, and (b) for 3-6 months (26%), possibly due

| TABLE 2 | Compilation of incidence of abnormal diagnostic findings |
|----------------|----------------|----------------|----------------|----------------|
|                | V1 (n) | % of V1 (n = 82) | All visits (n) | % of all visits (n = 98) |
| ECG            |         |                  |                |                      |
| ST-segment alteration | 17 | 20.7 | 23 | 23.5 |
| Ectopic beat   | 9 | 11.0 | 14 | 14.3 |
| Bundle branch block | 10 | 12.2 | 20 | 20.4 |
| Changes to previous ECG | 2 | 2.4 | 16 | 16.3 |
| Abnormal electric excitation | 2 | 2.4 | 10 | 10.2 |
| Echocardiography |         |         |                |                      |
| Reduced EF (<60%) | 8 | 9.8 | 20 | 20.4 |
| Pericardial effusion | 7 | 8.5 | 10 | 10.2 |
| Valvular heart disease | 10 | 12.2 | 19 | 19.4 |
| Wall motion disorder | 5 | 6.1 | 7 | 7.1 |
| Septal wall thickness (>10 mm) | 9 | 11.0 | 20 | 20.4 |
| Changes to previous echo | 1 | 1.2 | 12 | 12.2 |
| CMR            |         |         |                |                      |
| Reduced EF     | 5 | 6.1 | 12 | 13.3 |
| Pericardial effusion | 5 | 6.1 | 8 | 8.2 |
| Late enhancement | 12 | 14.6 | 20 | 20.4 |
| Wall motion disorder | 2 | 2.4 | 4 | 4.1 |
| Septal wall thickness (>10 mm) | 4 | 4.9 | 5 | 5.1 |
| Myocardial edema | 4 | 4.9 | 9 | 9.2 |
| 24 h-Holter ECG |         |                  |                |                      |
| Pathological result | 3 | 3.7 | 12 | 12.2 |
| Ectopic beat    | 10 | 12.2 | 25 | 25.5 |
| Polymorph ectopic beat | 2 | 2.4 | 9 | 9.2 |
| Couplets        | 4 | 4.9 | 8 | 8.2 |
| Triples         | 1 | 1.2 | 4 | 4.1 |
| Non-sustained ventricular tachycardia | 2 | 2.4 | 5 | 5.1 |

Note: Percentage value is due to all included cases at V1 (n = 82) rather or all included athletes for all visits (n = 98). More than one pathologic result per athlete over whole clinical course was only counted as one.

Abbreviation: EF, ejection fraction.
to hard diagnostic facts leading to a suspected diagnosis of myocarditis. For the most part, athletes accepted recommendations for training arrest of up to 3 months, whereas a training interruption of more than 3 months was only maintained in 10 cases (12.2%). Nevertheless, there were no serious adverse events during 1FU (like sudden death or cardiac arrest). Consequently, the chosen approach in terms of diagnostic work-up as well as RTS in our cohort seems to be safe.

4.2 Predictors for a worse outcome after 1FU

On an individual basis, it is not possible to predict the clinical course of “suspected” or proven myocarditis. Despite a multitude of easily available diagnostic possibilities (eg, laboratory results, echo, ECG), it is difficult to diagnose someone with suspected myocarditis, and particularly to differentiate between variations of normal and pathological results. For this purpose, athletes with even suspected myocarditis were deliberately included, as they representing the most common problem in everyday clinical practice. To improve clinical decisions when diagnosis of myocarditis is unclear, especially the interpretation of conspicuous results, predictors for a worse outcome would be helpful tools for risk stratification in clinical routine.

Our initial results only detected age as a predictor of a worse outcome at 1FU. Mean age of athletes who completely returned to sport (28.78 years) was significantly lower than that of athletes incompletely reintegrated (39.59 years). One can speculate that younger athletes have better resources for recovery. It is possible that gender may also influence outcomes. However, the level of significance was not achieved in our cohort. Gender distribution with only around 20% of the affected being women is probably correlated with gender specific differences of the sport disciplines in general. Whereas gender distribution for athletics showed almost balanced with 11 males vs eight females, big differences were present for soccer (18 males, 0 females) and cycling (10 males, three females). These findings fit well with data for number of members of the German Football Association (DFB) or German Athletics Association (DLV).

A large number of coincident abnormal diagnostic results (eg, abnormal results in more than two or three different diagnostic methods) might indicate highly suspicious myocarditis and could possibly predict worse outcomes. However, there is no correlation with RTS in our cohort, which might be caused by the low number of analyzed athletes.

Better prognosis and longer survival after diagnosis are seen for women with heart failure in general, as well as for myocarditis. Besides a worse reintegration in sport activity after 1 year, complaints of similar or worsen state of health after 1 year also occur more frequently in female athletes (35.3% vs 24.6%, \( P = .3308 \)). This might be explained by a more sensitive perception of symptoms in females and a more anxious behavior in terms of RTS.

There wasn’t any other of the diagnostic parameters predictive for incomplete reintegration. Although a trend for some of the parameters can be speculated, this lack of significance is possibly due to the low number of analyzed athletes at 1FU (n = 74).

4.3 Diagnostic work-up

The diagnostic work-up between the athletes differed widely. Predominately performed diagnostics at V1 were ECG, laboratory testing, and echo. Over the further clinical
course, the overall rate of exercise testing (57.1%), as well as the number of CMR and 24 h-Holter ECG, increased markedly.

Pericardial effusion was detected by echo in 10.2%, which was lower (20%) than described in patients with biopsy proven myocarditis. Wall motion abnormalities were seen in only 7.1% within our data.

A high number of athletes were scheduled for a CMR at V1 (32.8%). Within the clinical course, the total number of performed CMR increased up to 49.0%.
Abnormal results for wall motion disorders (echo: 7 cases; CMR: 4), pericardial effusion (echo: 10 cases; CMR: 8), and reduced EF (echo: 20 cases; CMR: 16) showed comparable results for echo and CMR. Lower numbers of abnormal findings using CMR can be explained by performance of CMR in a later stage of the clinical course. Therefore, we speculate that echo is not inferior to CMR for diagnostic purposes when carried out by experienced practitioners.

4.4 Diagnostic challenges in athletes

The clinical manifestations of myocarditis show a wide and heterogenic spectrum of symptoms. A viral infection is the leading cause for myocarditis (consistent with our data showing an infection rate of 72.0% in context).

ECG abnormalities can point to cardiac morphological changes, which are associated with sudden cardiac death. As Pelliccia et al showed in over 1000 athletes,19 a variety of abnormal ECG patterns occurred in 40% of the athletes, but structural cardiovascular abnormalities were only identified in 5%. These variations can be induced by sports activity through physiological cardiac remodeling. In our cohort, ECG abnormalities were seen in 23.5% with ST-segment alteration, 20.2% with bundle branch block, and 14.3% with ectopic beats. Changes to previous ECG (if available) occurred in 16.3% of all athletes. Compared with CMR results showing a high probability for myocarditis, for example, late enhancement (20.4%), EF reduction (16.3%), or myocardial edema (9.2%), the number of abnormal ECG did not seem to markedly overestimate diagnosis of myocarditis. Nevertheless, there is a danger to mistakenly diagnose healthy athletes as ill or to interpret a pathological ECG as non-pathological and induced by sports activity.

With regard to a wide range of unspecific symptoms, poor prognosis for RTS in the context of suspected myocarditis can also be explained by other possible differential diagnoses, such as overtraining, depression, psychosomatic disorders, or other chronic diseases. Episodes of overtraining were registered for at least 15 athletes over the last few years. Moreover, reduced intensity and duration of training, explored by the standardized questionnaire at 1FU, might be sometimes not directly a consequence of myocarditis, but rather of changes in interest or lack of time.

4.5 Prospects

Based on the described results of the nationwide German myocarditis registry, we could show that the chosen approach in terms of diagnostic work-up and RTS in our cohort seems to be safe. We expect that including additional athletes will enable us to develop criteria to guide individual decisions for sport participation in training and competition.

4.6 Limitation

Inclusion of athletes with suspected myocarditis in the registry is limited by the bias of the attending physician to make the diagnosis of suspected myocarditis. Therefore, the number of athletes might be under- or overrepresented. Moreover, the diagnostic approach is influenced by safety aspects within young and currently healthy athletes.

Analysis has been made additionally difficult by missing or implausible data, especially if many medical visits to different physicians prior to visiting a participating institute had to be recorded retrospectively. Furthermore, interpretation of borderline laboratory results becomes difficult, because of particularly implausible data caused by different reference values.

5 Perspective

Our nationwide registry is the first successfully implemented database of competitive athletes with suspected or
proven myocarditis. A high percentage of athletes present abnormal clinical or technical cardiac findings. However, most athletes return to sport within 1 year without negative consequences. There were no detected severe life-threatening adverse events at 1 FU. Consequently, even if there is missing evidence regarding how to treat athletes with suspected myocarditis in context of RTS, the chosen approach in terms of diagnostic work-up and decision regarding RTS seems to be safe. However, every 5th athlete was not completely reintegrated into sport activity at 1 FU, and duration and intensity of training were still reduced in one third of the athletes. Besides greater age, there is currently no parameter predictive for incomplete reintegration. In summary, treating athletes with suspected or proven myocarditis continues to be challenging but register data will help to get a more precise idea how to treat athletes with myocarditis.

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