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Sports cardiology screening, follow-up and physical fitness evaluation of special athlete populations

PhD thesis

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List of abbreviations

2,3-DPG – 2,3-Disphosphoglycerate

AV-block – atrioventricular block

BMI – body mass index

BPM – beats per minute

CCT – cardiac computer tomography

CK – creatine kinase

CMR – cardiac magnetic resonance imaging

COVID-19 – coronavirus disease 2019

CPET – cardiopulmonary exercise testing

CT – computer tomography

ECG – electrocardiogram

ESC – European Society of Cardiology

FEV1 – forced expiratory volume in the first second

FFMI – fat-free mass index

FIFA – Fédération Internationale de Football Association

HHF – Hungarian Handball Federation

HR – heart rate

hs Troponin T – high-sensitive Troponin T

IQR – interquartile range

mmHg – millimetre mercury

MRI – magnetic resonance imaging

PCR – polymerase chain reaction

pH – potential of hydrogen

PVC – premature ventricular contraction

Q1 – 1st quartile

Q3 – 3rd quartile

RAT – rapid antigen test

RER – respiratory exchange ratio

RPE – rate of perceived exertion

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

SCORE – Systematic Coronary Risk Evaluation score

SD – standard deviation

SDC – sudden cardiac death

USA – United States of America

$\dot{V}O_2$ – oxygen uptake

$\dot{V}O_{2max}$ – maximal oxygen uptake

1 Introduction

An ever-growing scientific evidence unequivocally demonstrates that engaging in regular physical activity plays a significant role in reducing the risk of a wide spectrum of diseases and significantly lowers all-cause mortality, thereby establishing itself as a cornerstone of preventive medicine and a key determinant of both longevity and overall quality of life. (1) Thereby, physical activity is generally advised to everyone, but the optimal type-, amount- and intensity of exercise differ depending on several conditions of the individual. In the presence of certain cardiovascular diseases, exhausting sport activities may be contraindicated. (2) Proper screening and examination, especially cardiovascular screening should be recommended for everyone who trains regularly, preferably prior they start or even restart sport activity. There are some underrated athlete populations who significantly contribute to sports, but usually does not get the proper preparticipation examinations, such as coaches or referees.

Many elite athletes are role models for crowds as people admire their achievements and feel loss when they cannot perform well in a competition. Furthermore, a sudden undesirable event, or even the sudden cardiac death of an athlete, could be a more shocking situation to many. With establishing a suitable screening system, even asymptomatic cardiovascular diseases could be recognized in time. The number of unwanted acute events and sudden cardiac death of athletes could be significantly reduced by participating in screenings assessing risk factors, detecting and monitoring structural diseases, as well as gradually increasing physical load instead of diving into high intensity training. (3)

Due to increasing number of elite athletes and individuals participating in regular leisure time physical activity, there is an increasing need for sports cardiology examinations. (4) In recent decades, we have more detailed knowledge about this fast-improving sub discipline of cardiology and sports medicine. However, there are still many questions and undiscovered parts of this field. For example, huge gaps in our knowledge are related to underrated athlete populations or even new diseases attacking humanity and affecting exercise capacity of the diseased patients.

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic, has brought unprecedented challenges and uncertainties in various aspects of human life, including the world of elite athletes. As the virus rapidly spread across the globe in late 2019 and early 2020, it became evident that no facet of society remained untouched, and the world of sports was no exception. In the wake of the pandemic, elite athletes, accustomed to rigorous training regimens and worldwide competitions, found themselves navigating an entirely new set of circumstances. Since the SARS-CoV-2 was a new virus, not even the short-term consequences of the infection were known at the beginning of the pandemic. For those athletes who suffered from COVID-19, later arose the question of when and how they could go on with their sports activities. (5-7)

1.1 Cardiovascular adaptation to sport

1.1.1 Definition of "sport" and athletes

The term "sport" is general and elusive; it includes professional elite athletes, recreational amateur athletes, everyday-need activities, and rehabilitation programs as well. In the Revised European Sports Charter by the Council of Europe, the definition of "sport" is the following: "[…] "sport" means all forms of physical activity which, through casual or organised participation, are aimed at maintaining or improving physical fitness and mental well-being, forming social relationships or obtaining results in competition at all levels." (8)

The definition of an athlete could be as challenging as the definition of "sport". (9) The European Society of Cardiology (ESC) defines an athlete as "an individual of young or adult age, either amateur or professional, who is engaged in regular exercise training and participates in official sports competition". (2) The terms amateur- and professional athletes refer to the legal classifications of athletes. The classification of "elite-", "competitive-", and "recreational athlete" are those individuals who train ≥10 hours/week, ≥6 hours/week, and ≥4 hours/week respectively, and intend to take part in competitions. (2) However, some groups of athletes are still not covered entirely by these definitions. For example, the referees participating in sports competitions do not take place in the matches to compete with each other. Still, their work requires good physical fitness in most of the sports to referee a game fairly and therefore they also need sports license, thereby, we could consider them as athletes. (10)

1.1.2 Classification of sports

Physical exercise can be divided into two major components: the dynamic- and the static component. Different types of sports contain these components in different proportions. Morganroth et al. grouped the athletes into two categories: those who perform isotonic exercise and those who do isometric exercise (11). Later, in the 36th Bethesda Conference recommendations, the types of sports were further divided, and nine classes were determined (12). In this classification, both the static and dynamic components were represented on a 3-point scale depending on the intensity of the given component required to perform the sport activity during competition (*Figure 1.*).

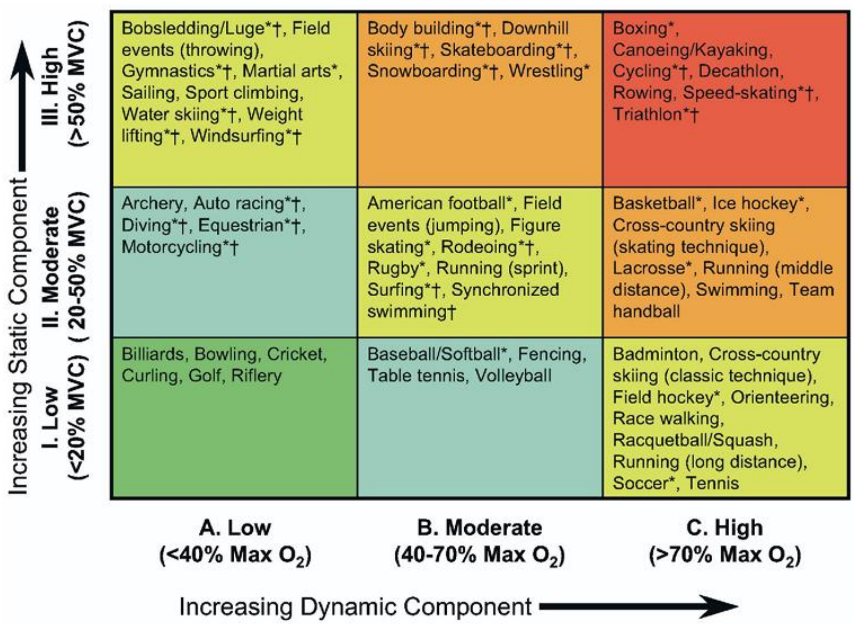

Figure 1. *Classification of sports by the 36th Bethesda Conference recommendations. (12) The sport-types are classified to nine classes based on their peak static and dynamic components during competitions. Abbreviations: MVC, percent of maximal voluntary contraction; Max O_2, percent of maximal oxygen uptake; *, danger of bodily collision; †, increased risk if syncope occurs*

In 2020, the ESC set up a more personalized classification. (2) First, the sport types were categorized into four classes based on the proportion of the static- and dynamic components: skill, power, mixed, and endurance. After that, each class was divided into three subclasses depending on the intensity of the given sports (*Figure 2.*). This recommendation drew attention to the necessity of individual classification since the intensity, duration, and proportion of different physical exercises could differ significantly within a type of sport.

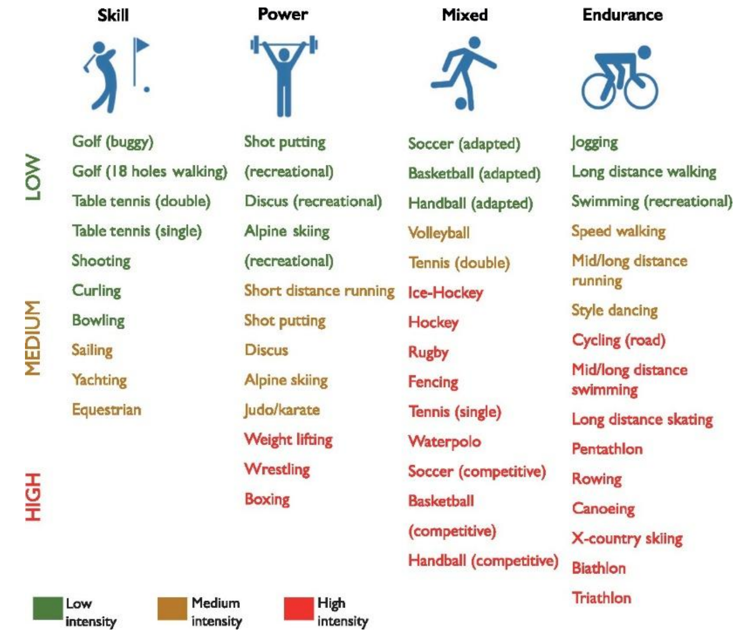

Figure 2. *Classification of sports by the European Society of Cardiology guideline. (2) The different sport-types are categorized into 4 classes and further divided by intensity.*

1.1.3 Short-term adaptation

During acute physical activity, increased skeletal muscle activation is accompanied by an increased energy demand; therefore, the oxygen and nutrient demand of the skeletal muscles increases. (13) The circulatory, respiratory, and metabolic systems must adapt to these changing conditions. Ventilation increases to ensure adequate oxygen supply to the tissues. To increase the ventilation properly for greater exercise, both breathing frequency and tidal volume increase during training. (14) Increasing the ventilation would not be enough to cover the oxygen needs of the working muscles if the oxygen content of the blood could not increase. An increase in perfusion is necessary not only in the lungs but also in the place of use, in the skeletal muscles, and in other organs involved in physical exertion so that the nutrients and oxygen required for terminal oxidation reach the target cells in sufficient quantities. (15) On the contrary to the increase in muscular perfusions, the circulatory redistribution induced by central and local neuroendocrine mechanisms decreases the circulation of the gastrointestinal system, as well as the blood supply of the skin, until the start of intensive heat release. (16) Local metabolic changes also help to achieve proper oxygen extraction in the muscles. With decreasing pH, 2,3-Disphosphoglycerate (2,3-DPG) release and increasing temperature, the dissociation of oxygen increases from the haemoglobin molecules locally. (17)

To achieve the higher perfusion of the working muscles, the performance of the heart needs to increase, which could be achieved by different mechanisms: on the one hand, it can be achieved through the chronotropic regulation, i.e., by increasing the heart rate and on the other hand, it can be achieved through the inotropic regulation, by increasing the contractility of the heart. (18) Dynamic and static load cause different acute changes. (19) As a result of dynamic load, stroke volume, cardiac output, heart rate and systolic blood pressure increase, while diastolic blood pressure does not change or decreases slightly. (20) In case of an acute static exercise, due to the changed breathing pattern and more pronounced breath holding, the superior vena cava volume is reduced. Therefore because of the reduced preload the filling of the chambers decreased and both right- and left ventricular end-systolic and end-diastolic diameters are reduced during the exercise. Since both of the systolic and diastolic dimensions are reduced the ejection fractions of the chambers do not change significantly. (21) While in case of an acute dynamic load, the volume load of the heart could be observed, during static exercises the pressure load is more pronounced. (22, 23)

1.1.4 Long-term adaptation

If physical exercise is performed regularly, the whole body adapts to it, from the molecular level of metabolic enzymes to phenotypic shifts in the muscles. (24, 25) Significant structural and functional changes also occur in the cardiovascular system. (26) The degree and proportion of these changes differs due to different types of training. Moreover, the proportion and characteristics of these changes are not only influenced by the sports activity itself but also by inherited, environmental and other influencing factors. For example, this may explain why the degree of adaptation is more pronounced in black and male athletes. While endurance training usually improves the ability to maintain physical activity for a longer distance or time, strength training mainly increases muscle size and enhances strength or speed. Previous studies suggest that high-intensity exercise increases mitochondrial activity, while greater training volumes increase the density of the mitochondria. (27, 28) Beside to the mitochondrial changes, the oxygen supply of the muscles increase with haematological adaptation and with increased capillary density. (29, 30)

1.1.5 Athletes' heart

In sports medicine, the term "athletes' heart" refers to the functional and structural adaptations of the heart to repeated exercise stimuli. (31) The first literature data detailed the morphological changes in the left ventricular dimensions and wall thicknesses, mainly eccentric hypertrophy, but further studies represented the sport adaptation of the right ventricle and the atria as well. (11, 32, 33) These adaptations results in physiological enlargement of the chambers of both sides without the decrease of the stroke volumes in rest. The resting ejection fractions are lower in athletes compared to the sedentary population, but due to the increased volumes of the heart chambers the stroke volume and the cardiac output are preserved. During physical activity more pronounced increase could be observed in the cardiac output in athletes, which is more advantageous to the myocardial work due to the increased ionotropic functions and lower heart rate increase at the same exercise. (34-36) Also the myocardial work is increased in athletes as functional adaptation to regular sports activity. (37) Furthermore, in case of athletes' heart, besides the morphological and functional changes, sport-related adaptations in the electrical system could be observed. (38, 39) Many sport-related alterations could be observed on the resting 12-lead electrocardiogram (ECG) as well. These changes could be sinus bradycardia, sinus arrhythmia, 1st degree atrioventricular block (AV-block), early repolarisation, etc. (40) As part of the whole-body adaptations, the autonomic nervous balance also changes with regular sport activity: the parasympathetic tone is increased, while the sympathetic activation is decreased in rest. (41) These autonomic nervous adaptations could be one cause for example of the decreased resting heart rate, beyond the ion channel changes, e.g. changes in the funny-channel functions. (42) As a result of structural, electrical, and functional alterations of the athlete's heart, significant differences can be observed compared to sedentary individuals also during resting and during physical activity as well. (43, 44) These changes are physiological adaptations to regular physical exercise, and after cessation of sports activity, during deconditioning, many of these revert to normal values. However, some pathological states, such as milder forms of hypertrophic cardiomyopathy, could be complicated to differentiate from the athletes' heart. In case of deconditioning – cessation of sport activity – these conditions do not revert in contrast to sport related changes. (2)

1.2 Importance of preparticipation screening

1.2.1 Sudden cardiac death

Sudden cardiac death (SCD) refers to an unforeseen, natural death resulting from a cardiac origin occurring within a short timeframe from the manifestation of symptoms without any prior condition that appears fatal. (45) The SCD is defined as sport-related when occurs during or happen shortly after physical exercise. (46-48) However, different registries define the sport-related SCD heterogeneously, thereby direct comparisons could be problematic. The underlying causes behind SCD differ with age in athletes. While in master athletes over 35-year-old, the most common cause of SCD is coronary artery disease, while among younger athletes, cardiomyopathies are found the most frequent basis for SCD. Regional differences are observed in the type of most often cardiomyopathies behind SCD. While in the United States of America (USA), hypertrophic cardiomyopathy, in Italy, arrhythmogenic cardiomyopathy is the most common cause of SCD in athletes. (49) Besides coronary artery disease and cardiomyopathies, other conditions, such as myocarditis, abnormal coronary artery anatomy, or channelopathies, could be the underlying fatal condition.

With proper preparticipation screenings, many of these diseases could be revealed in time. Unfortunately, despite proper screenings and detailed examinations, the first sign of specific conditions like abnormal coronary artery anatomy could still be SCD in a proportion of athletes.

1.2.2 Obligatory examinations

In many countries, preparticipation screenings are obligatory before performing sports activities or participating in a competition. (50, 51) In Hungary, preparticipation examinations are compulsory annually, or half yearly in youth and elderly age categories, to maintain valid sports license. These examinations include personal and family medical history, physical examination, 12-lead resting ECG, and urine laboratory examinations. (51, 52) Applying these examinations, the incidence of sport-related sudden cardiac deaths could be lowered to the incidence rate of the general population. (53) In case of positive findings during basic examinations detailed above, further evaluations are necessary, like cardiopulmonary exercise testing (CPET), 24-hour ECG recording, 24-hour ambulatory blood pressure measurement, echocardiography, or other imaging techniques.

In certain specialized sports disciplines, exercise stress ECG testing is mandatory for obtaining a medical license. UEFA level football referees represent one such example, where annual exercise ECG evaluation is required. (54)

1.2.3 Extended sports cardiology examinations

Applying extended sports cardiology examinations, cardiovascular diseases as well as other internal medicine diseases could be revealed. These examinations may include detailed laboratory testing, resting echocardiography, CPET. Cardiac magnetic resonance imaging (MRI) examinations, electrophysiological examinations and the entire repository of cardiology can also be used for the examination of athletes. (55, 56) Unfortunately, because of financial and medical capacity reasons, these examinations are limited to a few elite athletes, symptomatic- or diseased athletes, or scientific studies.

In case of elite athletes, extended cardiology screening, if performed regularly, is also suitable to follow up actual physical fitness status. With regular these screenings, we are able to compare the actual results with previous measurements. With these regular measurements, proper feedback on the effectivity of trainings could be given to the coaches and the athletes as well. (57) Moreover, recommendations could be made for training planning to achieve better performance and competition result. With these comparisons, we can also examine if the athletes got back to their top performance after an injury or infection. (58)

1.2.4 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing is a suitable method for extended cardiovascular examination and follow-up of athletes. With continuous 12-lead ECG monitoring during the CPET, the heart rate curve can be studied and pathological ECG findings can be revealed, e.g., arrhythmias and signs of ischaemic heart disease. (59-61) During the CPET, breath-by-breath gas analysis could be performed simultaneously, which also refers to pulmonary, cardiovascular and metabolic conditions as well. (62, 63) During the CPET measurements multiple parameters of the individual could be monitored, as the oxygen uptake ($\dot{V}O_2$), the carbon-dioxide production, the ventilation and the lactate levels. These values could be summarised in the 9 Wassermann-graphs. The exercise measurements could be performed on various ergometers, like bicycle ergometers or treadmill ergometers. If the measurements are performed on a treadmill ergometer, the slope and the speed of the belt could be controlled. With different settings we could provide a more sport-type specific protocol for the athletes. (64)

Beyond cardiovascular screening, CPET examinations are also suitable for physical fitness follow-up. With the provided Wassermann-graphs, different thresholds could be determined, for example the aerobic- and anaerobic thresholds, also the maximal oxygen uptake ($\dot{V}O_{2max}$) or the lactate profile of an athlete. (63) Also results from different time points could be compared to each other, thereby the changes in the performance of the athletes could be easily followed-up. These measurements could help for the athlete and also for their coaches in training planning and shape timing.

1.2.5 Examinations after infection

Infections, including viral illnesses, pose significant challenges for elite athletes, often necessitating temporary suspension of the medical sports license during acute phases. (65) After full recovery, additional examinations are not necessary most of the time. If the athlete has long-lasting symptoms or severe infection, repeated preparticipation screening could be advised for safe return-to-play. The recent guideline highlights that in case of an inflammatory myopericardial syndrome, restriction of the physical activity is necessary for at least 1 month to reach clinical remission, but it can last longer depending on individual cases. (66)

These infections may involve multiple organ systems beyond the cardiovascular apparatus, e.g., Epstein-Barr virus infection can manifest with splenomegaly or hepatopathy. Similarly, COVID-19 is associated with a spectrum of complications, including pulmonary, cardiovascular, neuropsychiatric, and musculoskeletal sequelae, among others. (67) A comprehensive, holistic clinical approach is essential for athletes to mitigate life-threatening risks. Long-term symptoms may persist post-acute phase due to organ damage, dysregulated inflammation, autoimmunity, microvascular dysfunction, or ongoing viral activity These long-term effects vary depending on the pathogens and on the individual responses. (68) The long-lasting symptoms could cause an additional reduction in the physical capacity of the athletes beyond the duration of training cessation. The decrease in exercise tolerance could also affect the return-to-play decisions. (69, 70)

CPET measurements offer a valuable method to objectively assess fitness status post-infection, including SARS-CoV-2, and were integral to return-to-sport recommendations in certain athletic populations from the early stages of the pandemic. (71-73)

1.3 Special athlete populations

Most of the available scientific literature refer to adult, mainly male elite athletes, who perform high intensity trainings for a long time period. However, many individuals do their sport activity in a lower intensity or not for intention to complete in high level competitions. These athletes could be leisure time athletes, sport professionals who are not the athletes but contribute significantly to the sport events (for example referees) and also athletes who are recovering from or constantly suffering from a disease. Moreover, youth athletes and female athletes are also underrepresented in the scientific literature.

While the above-mentioned extended sports cardiology screenings could be achievable mainly to elite athletes through their sports associations/federations, many other athletes could not access to these examinations.

1.3.1 Referees

A good physical capacity is required for the referees, since it could influence the decision-making in match situations. (74) In the literature, there is only insufficient information regarding the physical fitness of referees, but those results are about outdoor sports mainly, primarily examining football referees. At greater loads, inappropriate physical fitness could negatively influence cognitive functions, which is essential to refereeing fairly always according to the official rules and regulations of the refereed game. (75) In addition to physical load, the inseparable mental stress also exerts a significant impact on the decision-making of the referees. (76, 77) In Hungary, handball referees must pass multiple tests annually; these include shuttle running, 12-minute continuous running, and rule- and video tests. The minimum requirements are determined by the Hungarian Handball Federation (HHF). Existing literature data suggest that the decision-making of the referees is not only determined by the time spent in the anaerobic phase but rather by the rating of perceived exertion (RPE), which could be lowered by regular training. (78) Within a unique cooperation between the Heart and Vascular Center of Semmelweis

University and the Referee Subcommittee of the HHF, Hungarian elite handball referees had the opportunity to participate in an extended sports cardiology screening program and physical fitness evaluation in our Clinic.

1.3.2 Post-SARS-CoV-2 athletes

The SARS-CoV-2 pandemic created an extraordinary situation. For those athletes who suffered from a SARS-CoV-2 infection in the first years of the pandemic, strict recommendations and regulations were implemented to return-to-sport activity (*Figure 3.*). (73, 79, 80) Initial data suggested a large proportion of myocarditis among patients due to SARS-CoV-2 infection; however, further studies described considerably fewer cases. (7, 81, 82)

In Hungary, the first regulations regarding competitive sport activity were created in 2020. (71, 83) At this period, athletes lost their sports medicine license due to the infection and, even in case of an asymptomatic infection, cardiology examinations were necessary before return-to-sports after a minimum of three weeks cessation of training. These examinations included resting ECG, echocardiography and laboratory blood examinations with troponin level measurements. In case of positive findings, further examinations were prescribed, such as computer tomography (CT), MRI or 24-hour Holter-ECG. (65, 71) Due to the increasing number of scientific results showing that SARS-CoV-2 infection does not cause significant pathologies in most of the otherwise healthy young athletes, these regulations were updated in 2022. (72) Since then, two weeks after the start of COVID-19, a resting ECG and a troponin level measurement were satisfactory for return-to-sports in asymptomatic individuals. However, in the statement for national team athletes, echocardiography examination was still mandatory. The CPET examinations were allowed to perform after a negative troponin blood test. In both protocols, regulations were the same as for the athletes for referees working in high-intensity physical environment, like football and handball referees.

We had an opportunity to examine a large population of elite athletes from various types of sports after the infection but before they restarted their training. They were also invited to participate in our study to examine the long-term effects of a SARS-CoV-2 infection on their sports carrier.

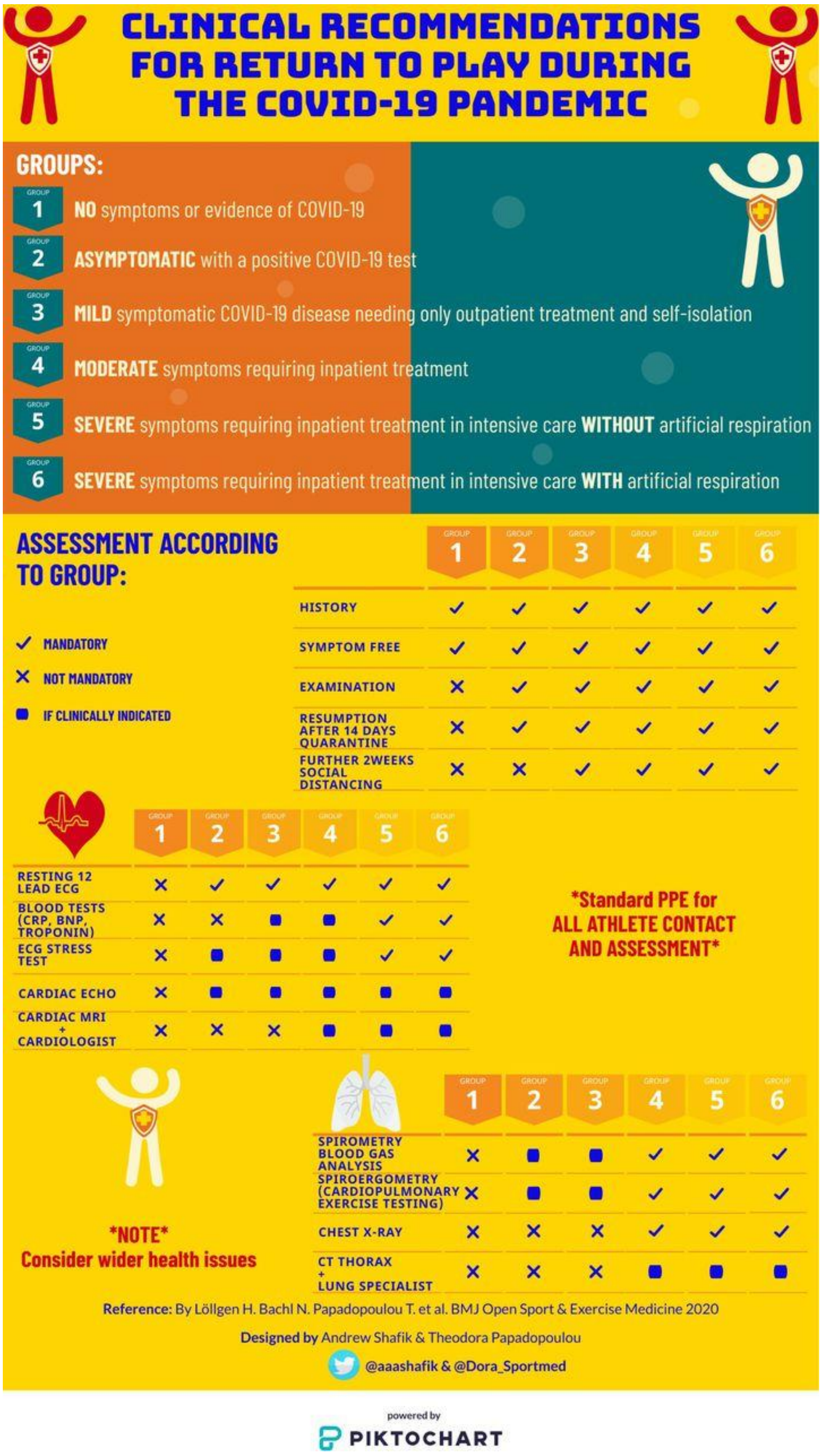

Figure 3. *Infographic about return-to-sport after SARS-CoV-2 infection. (73, 84) The risk assessment was based on the severity of the infection and the recommended examinations were based on the initial classification.*

2 Objectives

At the Heart and Vascular Center of the Semmelweis University, we had three main aims during our examinations of athlete groups underrepresented in previous research:

2.1 Evaluation of cardiovascular risk factors of elite handball referees

We have previous data about the cardiovascular risk factors among elite athletes, but we needed more information about the referees. In our cross-sectional study, we aimed to evaluate the prevalence of cardiovascular diseases and risks among top Hungarian handball referees.

2.2 Examination the physical fitness of elite handball referees

Although we have information about the physical fitness of elite athletes, we needed more data about the referees who referee their games. In our research, we aimed to examine the top 100 Hungarian handball referees to assess their physical fitness.

2.3 Examination of the long-term effects of a SARS-CoV-2 infection on sport performance and physical fitness of elite athletes

Many publications are available about the short-term impacts of a SARS-CoV-2 infection; however, we needed information about the longer-term effects of a COVID-19 disease on physical fitness. We aimed to examine elite athletes three months after a SARS-CoV-2 infection and to compare these results with their measurements before the pandemic in a cross-sectional and self-controlled study.

3 Methods

3.1 Participants

3.1.1 Handball referee examinations

In our research, 100 asymptomatic elite referees of the Hungarian Handball Federation of both sexes, aged 18 and above, were examined. Any symptoms of internal-, cardiovascular-, or musculoskeletal diseases or suspension of regular physical activity in the last six months are counted as exclusion criteria. All the examined referees were Caucasian. The referees were selected in cooperation with the Referee Subcommittee of the HHF to include the 100 best Hungarian handball referees in this study.

3.1.2 Athletes post-SARS-CoV-2 infection

In one year from 2020 autumn, cardiology control examinations and CPET examinations were carried out following returning to high-intensity training after suffering a SARS-CoV-2 infection in 183 athletes. Asymptomatic elite athletes (adults training ≥ 10 h/week) and all athletes with positive findings or ongoing symptoms during the first cardiology check-up were invited to participate in the study. Athletes with previously known cardiovascular diseases (excluding hypertension) or musculoskeletal symptoms were excluded from the study.

Detailed CPET analysis was carried out on 165 asymptomatic elite athletes. Moreover, the results of the cardiovascular evaluation of 18 athletes, either symptomatic or with previous pathological findings, were also examined, however they were evaluated separately and individually from the asymptomatic elite athletes.

3.1.3 Consent and ethical license

Before the studies, all participants gave written informed consent to the examinations and the research purposes after being provided verbal information and answers to all the arising questions. The Medical Research Council of Hungary approved the studies (No.: 13687-1/2011-EKU and IV/9697-1/2020/EKU) according to the Ethical Guidelines of the Helsinki Declaration and to Good Clinical Practice.

3.2 Procedures

3.2.1 Resting examinations in both studies

All measurements were performed at least 12 hours after the last training, competition or refereeing.

Personal and family history was taken by a detailed questionnaire and a personal interview conducted by a sports cardiologist. Positive family history was considered in accordance with the Professional Guideline of the Hungarian National Institute of Sports Medicine. (85) Following a physical examination and resting blood pressure measurement, a standard 12-lead ECG was recorded in a resting, lying position and analysed according to the current guidelines (CardioSoft PC, GE Healthcare, Finland). (40) The evaluation of blood pressure values was carried out in concordance with the European guideline in force at the time of the measurements: resting values over 139 mmHg systolic or 89 mmHg diastolic blood pressure were considered hypertensive. (86)

The fasting laboratory examination contained complete blood cell count, ions, detailed lipid analysis, liver and kidney panel, iron profile, creatine kinase (CK), lactate dehydrogenase, glucose, haemoglobin A1C, and thyroid panel. All the laboratory examinations were carried out in the same laboratory with the same equipment. Lipid cut-off values were determined per the ESC/EAS guidelines in force at the time of the execution of the study. (87) The cut-off values for slightly elevated CK were between 190.0 U/l and 500.0 U/l, whereas over 500.0 U/l was taken as a markedly elevated CK. Cardiac necroenzyme levels were measured from blood samples (cobas e 411 analyzer, ROCHE Hungary Ltd, Hungary; Elecsys Troponin T hs, Roche Diagnostics International AG, Switzerland).

Body-composition analyses were carried out by bioelectrical impedance measurements (Bodystat 1500 MDD, Bodystat Ltd, UK; InBody 770, InBody Co. Ltd, South Korea). Body mass index (BMI) was calculated as BMI [kg/m^2] = body weight [kg] / body height^2 [m^2], and fat-free mass index (FFMI) as FFMI [kg/m^2] = body fat-free weight [kg] / body height^2 [m^2]. (88)

Routine echocardiography was performed according to the guidelines in force at the time of the examinations (Vivid E95, GE Vingmed Ultrasound, Horten, Norway). (89)

When indicated, Holter ECG (Cardiospy, Labtech Ltd., Hungary), ambulatory blood pressure monitorization (Card(X)plore, Meditech, Hungary), cardiac MRI (CMR; Achieva, Philips Medical Systems, The Netherlands; Siemens Magnetom Area, Siemens Healthineers, Germany), cardiac CT (CCT; Brilliance iCT256, Philips Medical Systems, The Netherlands), dobutamine stress echocardiography or cardiac percutaneous coronary intervention were also performed. A cardiology expert analysed the results according to the available guidelines.

3.2.2 Additional resting examinations in handball referees

For the evaluation of fatal cardiovascular risk among the handball referee, the ESC Systematic Coronary Risk Evaluation score (SCORE) was calculated in every cases. Since all the examined referees were Hungarian, the European High Risk Chart was used for the calculations. (90)

3.2.3 Additional resting examinations in athletes post-SARS-CoV-2 infection

The SARS-CoV-2 infection was confirmed by polymerase chain reaction (PCR) or by rapid antigen test (RAT); these tests were carried out individually prior to the study and were necessary for the enrolment. Athletes underwent cardiology screening in accordance with the return-to-sport recommendations 2-3 weeks after the infection. (71, 80) In case the first screenings were negative, athletes were advised to build up their regular training step-by-step. Athletes were invited for the second examination between 2 and 4 months after the SARS-CoV-2 infection, after returning to their current maximal intensity training.

A detailed questionnaire was implemented to record the data on SARS-CoV-2 infection and sports activity. The severity of the acute infection was classified following the recommendations of Löllgen H et al. (73) Control echocardiography was also performed.

3.2.4 Exercise examinations

To ensure similar conditions for all referees, measures took place in the morning hours during the playoff period of the season in an air-conditioned laboratory with constant temperature and humidity.

For the referee examination the CPET was implemented on a treadmill ergometer (T-2100, GE Healthcare, Finland) using an incremental protocol starting with a 1-minute flat walk of 6 km/h, followed by continuous 10 km/h uphill running with an increasing slope of 1.0% every minute until exhaustion.

In case of the post COVID-19 athletes the maximal CPET examinations were carried out on the same treadmill with sport-specific incremental protocols (starting with a 1-min sitting resting phase, followed by 1–2 min flat walk of 6 km/h as a warm-up, then by continuous 8–10 km/h uphill running with an increasing slope of 1.0–1,5% every minute until exhaustion). For athletes with prior CPET data available in our Clinic from before the SARS-CoV-2 infection, the same CPET protocols were applied to both examinations, and comparisons were made between pre- and post-SARS-CoV-2 CPET measurements. The pre-SARS-CoV-2 CPET examinations were conducted across different training phases (off-season, preparation period, peak performance). In contrast, the post-SARS-CoV2 CPET examinations were carried out after 2–3 weeks of training break during SARS-CoV-2 infection followed by a step-by-step rebuilding of training to reachieve peak performance. For inclusion into the study, it was mandatory to achieve maximal intensity at the CPET examination after the infection and, in the case of CPET comparisons, in the CPET examination before the infection as well.

The maximal intensity was considered to be achieved if the athlete reported maximal subjective fatigue and either the respiratory exchange ratio (RER) was over 1.1 or flattening could be seen in the oxygen uptake and the heart rate curves. After stopping running, measurements were continued during a 1-minute 4 km/h walk and a further 4-minute rest in sitting position. (91, 92) Breath-by-breath gas analysis was carried out using an automated cardiopulmonary exercise system (Respiratory Ergostik, Geratherm, Germany). Prior to the CPET examination basic lung function measurements, with forced expiratory volume in the first second (FEV1) determination were carried out in every case.

The reference values for non-athletes were integrated into the system by the manufacturer, considering sex, age, height, and weight. During the CPET examinations, continuous ECG monitorization was carried out (CAM-14 module, GE Healthcare, Finland), and the estimated maximal heart rate (HR) was calculated as 220-age. (2)

The HR values were calculated as the average of 10-second measurements. Blood lactate levels were measured from fingertip capillary blood drops at rest, during the exercise every second minute, at maximal load, and in the fifth minute of the cool-down (Laktate Scout 4+, EKF Diagnostik, Germany). The anaerobic threshold was determined based on the lactate levels and the kinetics of the recorded Wasserman graphs. (93) All CPET data were reported as an average of 10 seconds. All examinations and data collection were supervised by a cardiology and sports medicine specialist.

3.3 Statistical analysis

Statistical analyses were performed using dedicated software (Microsoft Excel, Microsoft Corporation, USA; Real Statistics Resource Pack software (Release 7.6), Copyright (2013–2021) Charles Zaiontz). (94) Descriptive statistical values are shown as number (percentage), mean ± SD for normally distributed parameters, and median (interquartile range: 1st quartile –3rd quartile (IQR: Q1–Q3)) for non-normally distributed parameters. The normality of the valuables was tested with the Shapiro–Wilk test and the homogeneity of variances was tested with F-test. Comprehensive statistical analysis was carried out with the Fischer exact test, Chi-square test, Wilcoxon rank sum test (Mann–Whitney U test) or two-tailed unpaired Student's t-probe with equal or unequal variance form, paired Student's t-test or Wilcoxon Signed Rank Test, depending on the data. Correlation analysis was performed via the Pearson correlation. Statistical significance was determined if $p < 0.05$. All missing data were proved to be missing-completely-random; thereby, available-case-analysis was carried out for the statistical evaluation.

4 Results

4.1 *Elite handball referee studies*

4.1.1 Referee population

The studied 100 elite handball referees (age: 29.6 ± 7.9 years, age range: 18–46 years, male: 64.0%) trained an average of 4.3 ± 2.0 hours/week (range: 1–11.5 hours/week) (*Table 1*). In all, 51.0% participated as referees in the first division, and 49% in the second division of the Hungarian National Handball League. A 16% of them were also official referees in either the International or the European Handball Federations. Previously, 39.0% had also played handball as athletes in the first or second divisions.

Table 1. *Basic parameters of Hungarian elite handball referees according to the division of refereeing.(95, 96)*

Continuous variables are presented as means ± SD, categorical variables are reported as number and frequencies (%). Abbreviations: h/w, hours/week; BMI, Body Mass Index; FFMI, Fat-free Mass Index. Statistical analysis was carried out between the First and Second division referees. Italics indicates statistical significance.

	All referees	First division referees	Second division referees	p-value
Participant (%)	100 (100.0)	51 (51.0)	49 (49.0)	-
Male (%)	64 (64.0)	39 (76.5)	25 (51.0)	*0.008*
Age (year)	29.0 ± 7.9	33.0 ± 8.1	24.8 ± 5.2	*<0.001*
Training (h/w)	4.3 ± 2.0	3.8 ± 2.0	4.8 ± 2.0	*0.006*
Height (cm)	178.0 ± 8.1	179.6 ± 8.9	176.4 ± 7.0	0.055
Weight (kg)	78.0 ± 13.3	81.5 ± 13.6	74.3 ± 12.0	*0.005*
BMI (kg/m^2)	24.5 ± 2.7	25.1 ± 2.3	23.8 ± 3.0	*0.016*
Body fat (%)	18.7 ± 6.6	16.4 ± 5.4	21.0 ± 6.9	*<0.001*
FFMI (kg/m^2)	19.9 ± 2.6	21.0 ± 2.1	18.8 ± 2.7	*<0.001*
Former elite player (%)	39 (39.0)	23 (45.1)	16 (32.7)	0.202

4.1.2 Personal and family history

None of the examined referees had any cardiovascular symptoms. Regarding the cardiovascular risk factors or diseases, 24% had a positive personal or family history. Sudden cardiac death due to acute myocardial infarction of their parents or grandparents at younger ages was found in the family history in two cases. In one case, the personal history was positive due to syncope. At the time of the study, 21.0% of the referees were smoking (male: 15.0%). Surprisingly, those who played handball previously at higher levels had a higher tendency for smoking compared to the non-elite players (25.6 vs. 18.0%, $p = 0.45$). They had no prior established cardiovascular diseases, except for treated arterial hypertension in 4.0% and ablated AV re-entry tachycardia in 1.0%.

4.1.3 Physical examination

No significant physical abnormalities were found during routine examinations. Mean height, body mass, BMI, and body fat percentage are shown in *Table 1*. Without increased BMI, 5.0% of the referees proved to have an isolated increase in body fat percentage. Due to fat-free mass increase, 31.0% had higher BMI values with having their body fat values in the normal range. Considering both higher body fat and BMI increase, 10.0% were overweight (male: 9.0%), whereas obesity was diagnosed in 3.0%, all males (*Figure 4*). Obesity and overweight tended to be more frequent among those referees who did not play previously at elite levels than those who played (16.4 vs 7.7%, $p = 0.24$).

Resting mean systolic blood pressure was measured as 133.5 ± 16.2 mmHg, while resting mean diastolic blood pressure was 82.4 ± 10.5 mmHg. Based on the recommendation in force at the time of the execution of the study, isolated elevation of the systolic blood pressure was found in 17.0% of the referees, while 9.0% had isolated diastolic blood pressure elevation. Both systolic and diastolic resting blood pressures were higher in 12.0%. Elevated values of the resting blood pressure were measured more often in the former non-elite handball player group compared to the former elite players (49.2 vs 20.5%, $p = 0.006$).

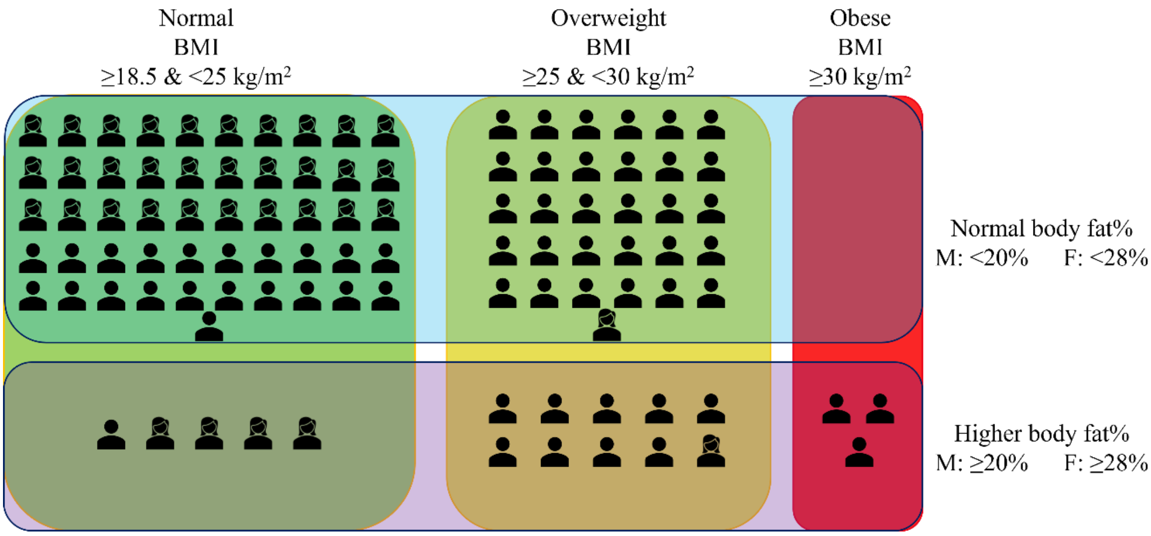

Figure 4. *Distribution of the referees according to BMI and body fat percentage. Abbreviations: BMI, Body Mass Index; body fat%, body fat percentage; M, male; F, female*

4.1.4 Resting ECG

The mean resting HR was 78.8 ± 11.8 BPM. By the results of the resting 12-lead ECG recordings, isolated QRS voltage criteria for left ventricular hypertrophy were found in 2.0%, incomplete right bundle branch block in 47.0%, sinus bradycardia in 10.0%, sinus arrhythmia in 6.0%, first degree AV-block in 2.0% as normal, sports-related ECG changes. Out of the 55 referees who had at least one sport-related physiological ECG changes, 37 were male. Right axis deviation appeared at 2.0% and left axis deviation at 14.0%. These grey zone ECG changes were isolated in all of the cases, requiring no further evaluation according to the current guidelines. Pathological resting inferior ST-depression was found in 1.0%, and pathological T-wave inversion or biphasic T-waves were recorded in 6.0% of the cases. Sinus tachycardia was detected in 2.0% (heart rate: 102 BPM and 130 BPM) on the resting ECG, combined with monomorphic ventricular bigeminy in one case. No other grey zone or pathological ECG abnormalities were detected on the 12-lead ECG. In total, ten referees had one or two pathological ECG changes, and four of them were male.

4.1.5 Laboratory examinations

The measured values of the laboratory blood examinations are represented in *Table 2*. Due to physical activity, the mean level of serum CK was slightly elevated. Individually, slightly elevated values were measured in 26.0%, and markedly elevated values in 4.0%. Dyslipidaemia requiring lifestyle changes was found in 38 patients; 33 out of them were male, while lipid-lowering medication was indicated in 3 cases. Decreased free iron levels were found in 20.0% of the referees, while total iron-binding capacity increased in 16.0%, transferrin increased in 5.0%, transferrin saturation decreased in 16.0%, and ferritin level decreased in 6.0% of the cases. A lower red blood cell count was found in nine female referees, while a lower haemoglobin level in nine females as well. All these cases were attributed to iron deficiency. No other significant laboratory test deviations were found.

Table 2. *Results of the blood examinations in elite Hungarian handball referees (96)*

Continuous variables are presented as means ± SD. The reference values were established based on the local laboratory.

	Mean ± SD	**Reference value**
Creatine kinase (U/l)	230.2 ± 399.1	3.0 – 190.0
Total cholesterol (mmol/l)	4.6 ± 0.8	2.0 – 5.2
LDL cholesterol (mmol/l)	2.9 ± 0.8	<3.3
Triglycerides (mmol/l)	1.1 ± 0.8	<2.2
HDL cholesterol (mmol/l)	1.6 ± 0.4	0.9 – 1.4
Free iron (mmol/l)	18.5 ± 7.4	12.5 – 32.2
Total iron-binding capacity (umol/l)	70.5 ± 13.0	45.0 – 81.0
Transferrin (g/l)	2.9 ± 0.5	2.0 – 3.6
Transferrin saturation (%)	23.0 ± 11.8	16.0 – 45.0
Ferritin (ug/l)	112.0 ± 96.8	20.0 – 250.0
Red blood cell (10^{12}/l)	4.9 ± 0.4	4.3 – 5.9
Haemoglobin (g/l)	145.8 ± 15.5	130.0 – 180.0

4.1.6 *Systematic coronary risk estimation*

Most of the referees, 96.0% had a SCORE point <1, while four referees had a SCORE point between ≥1 and < 5. All of them were male with personal history of smoking. (*Figure 5.*)

Figure 5. *SCORE chart of high risk countries. Values indicating the risk of a fatal cardiovascular event in 10 years. On the SCORE chart the referees, who had ≥1 point are marked with a circle. Adapted from (90)*

4.1.7 *Echocardiography*

The average left ventricular ejection fraction was measured as 59.9 ± 3.3%, while the average posterior and interventricular septal end-diastolic wall thicknesses were 8.6 ± 1.4 mm and average: 9.5 ± 1.5 mm respectively. Grey zone posterior wall thickness was found in 2.0%, and grey zone interventricular septal wall thickness in 3.0%; all these changes were found in males. Regarding the pathological changes, first-grade mitral valve insufficiency was seen in 6.0%, and mitral prolapse syndrome in 3.0%. Interatrial septal aneurysm was detected without shunt flow in one patient, and increased trabecularization was seen in another case. Dilated aortic root was detected in 2.0% of the cases; one of these patients also had a bicuspid aortic valve. No cases of functional deviation were found regarding the right ventricles, but one athlete had increased right ventricular dimensions. Pathological echocardiographic changes affected six male and six female patients.

4.1.8 Cardiopulmonary exercise testing

On our running protocol, the average running time was 9.3 ± 2.9 min for all referees (range: 4.3 – 15.7 min), with a maximal HR of 187.2 ± 11.1 BPM (range: 157–210 BPM,), an average of 98.1 ± 4.6% of the calculated individual maximal values. The referees achieved a maximal ventilation of 128.1 ± 29.7 l/min (range: 69.0–207.0 l/min), with $\dot{V}O_{2max}$ of 44.6 ± 6.1 ml/kg/min (range: 25.3–62.4 ml/kg/min) and a peak lactate level of 9.2 ± 3.2 mmol/l (range: 3.1–18.9 mmol/l). On average, the referees achieved their anaerobic threshold at 56.1 ± 15.8% of the exercise time, with 91.5 ± 6.5% of their maximal HR and with 86.5 ± 8.2% of their $\dot{V}O_{2max}$. Data are shown in *Table 3*. There was no significant difference in the exercise time between males and females (respectively, 9.6 ± 2.8 vs. 8.8 ± 2.8 min; $p = 0.17$), while $\dot{V}O_{2max}$ proved to be higher in male referees (respectively, 47.0 ± 5.7 vs. 40.4 ± 4.3 ml/kg/min; $p < 0.001$).

In all the parameters mentioned above, significant individual differences could be observed among the referees, as presented in *Figure 6*. Exercise time ranged between 4.3 and 15.7 min (*Figure 7.*), $\dot{V}O_{2max}$ between 25.3 and 62.4 ml/kg/min (*Figure 8.*), and anaerobic threshold time between 2.3 and 12.0 min. In most cases, the measured values of relative $\dot{V}O_{2max}$ and ventilation overreached the estimated non-athlete reference values specified by the manufacturer.

Table 3. *Cardiopulmonary exercise testing results of Hungarian elite handball referees according to the division of refereeing. (95)*

Continuous variables are presented as means ± SD. Abbreviations: HR_{rest}, resting heart rate; HR_{max}, maximal heart rate; HR_{AT}, heart rate at the anaerobic threshold; BPM, beats-per-minute; Lac_{peak}, peak lactate; $\dot{V}O_{2max}$, maximal oxygen uptake; $\dot{V}O_{2AT}$, oxygen uptake at the anaerobic threshold; VE_{max}, maximal ventilation; AT, Anaerobic threshold. Italics indicates statistical significance between the First and Second divisions.

	All referees	First division referees	Second division referees	p-value
HR_{rest} (BPM)	79.0 ± 12.6	78.7 ± 11.1	79.3 ± 14.1	0.745
Exercise testing time (min)	9.3 ± 2.8	7.7 ± 2.2	11.0 ± 2.4	*<0.001*
HR_{max} (BPM)	187.2 ± 11.1	183.3 ± 15.9	190.0 ± 10.2	*0.012*
Lac_{peak} (mmol/l)	9.2 ± 3.2	9.0 ± 3.6	9.5 ± 2.6	0.421
$\dot{V}O_{2max}$ (ml/kg/min)	44.6 ± 6.1	45.1 ± 5.6	44.0 ± 6.7	0.291
$\dot{V}O_{2max}$ compared to reference (%)	124.9 ± 14.3	126.5 ± 13.6	123.3 ± 15.0	0.275
VE_{max} (l/min)	128.1 ± 29.7	134.0 ± 28.1	121.8 ± 30.3	*0.016*
VE_{max} compared to reference (%)	119.6 ± 17.2	120.9 ± 15.0	118.2 ± 19.4	0.430
AT time (min)	5.1 ± 1,9	4.4 ± 1.7	5.8 ± 2.0	*<0.001*
AT time / total time (%)	56.1 ± 15.8	58.7 ± 16.2	53.4 ± 15.2	0.103
HR_{AT} (BPM)	171.0 ± 14.4	168.4 ± 14.9	173.8 ± 13.4	*0.013*
HR_{AT} / HR_{max} (%)	91.5 ± 6.5	92.8 ± 11.2	91.4 ± 5.1	0.245
$\dot{V}O_{2AT}$ (ml/kg/min)	38.3 ± 5.5	39.4 ± 5.3	37.1 ± 5.5	*0.036*
$\dot{V}O_{2AT}$ / $\dot{V}O_{2max}$ (%)	86.5 ± 8.2	88.1 ± 7.7	84.8 ± 8.4	*0.049*

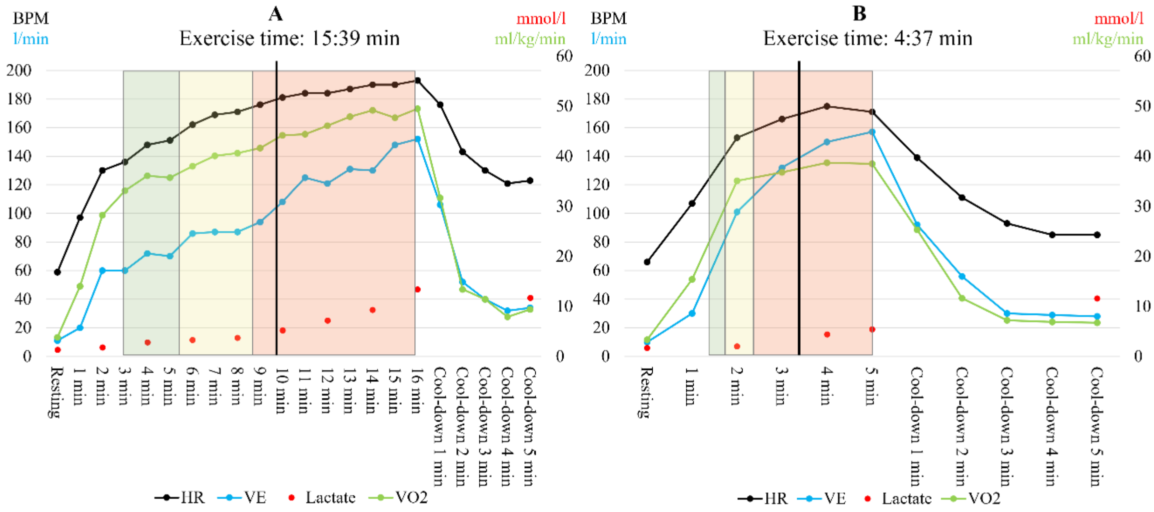

Figure 6. *Representative cardiopulmonary exercise testing curves of the referees. (95) A) Cardiopulmonary exercise testing (CPET) results of a male referee who achieved the longest time in our sport-specific running protocol, B) CPET curves of a male referee who was among those who achieved the shortest running time. On the graphs, heart rate (HR, black line), ventilation (blue line), lactate values (red dots), and oxygen uptake (green line) are indicated. The vertical black line represents the anaerobic threshold, while the green, yellow, and red boxes indicate the HR intensity levels calculated from the achieved maximal HR (respectively, moderate, submaximal, and maximal intensity). Abbreviations: HR, Heart rate; VE, Ventilation; V̇O2, oxygen uptake; BPM, beats-per-minute.*

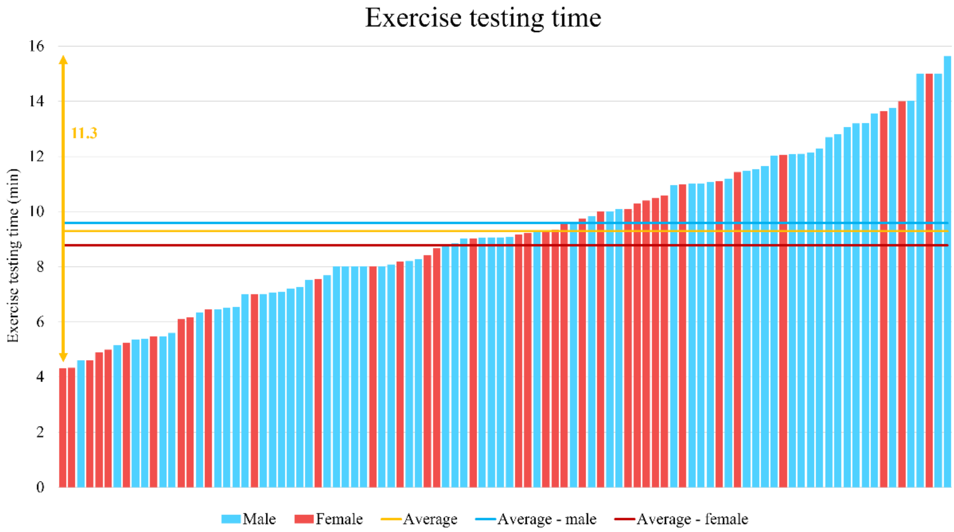

Figure 7. *Exercise running times of elite Hungarian handball referees on a sport-specific protocol. (95) Each bar represents a referee. Male referees are shown with blue, female referees with red bars. The blue, red, and yellow lines represent the average running times for male, female, and all referees, respectively. The yellow double arrow highlights the difference between the longest and shortest running times of the referees.*

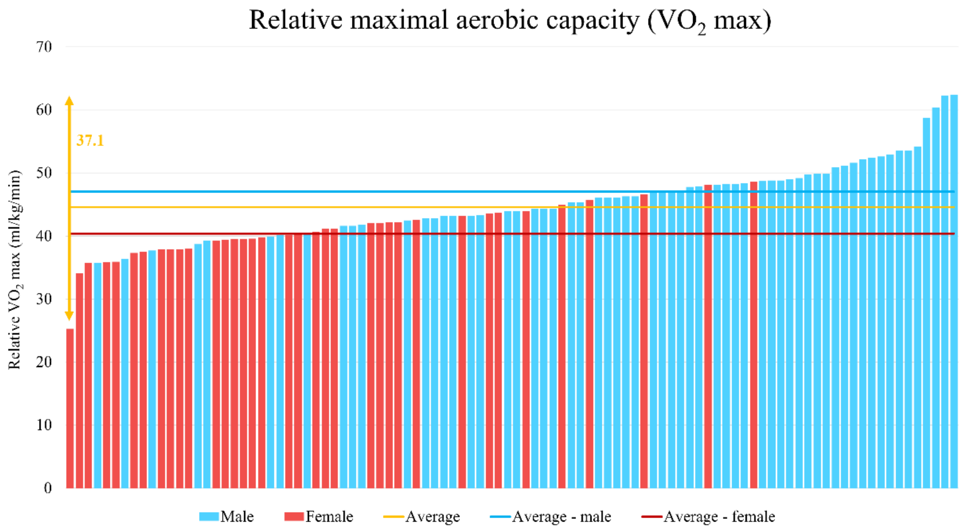

Figure 8. *The relative maximal oxygen uptakes of elite Hungarian handball referees on a sport-specific protocol. (95) Each bar represents a referee. Male referees are shown with blue, female referees with red bars. The blue, red, and yellow lines represent the average values for the male, female, and all referees, respectively. The yellow double arrow highlights the difference between the highest and lowest relative maximal oxygen uptake values of the referees.*

The most common pathological changes were hypertensive exercise or recovery blood pressure values in 10.0%, multiple premature ventricular contractions (PVC) during exercise or recovery in 8.0%, and pathological ST-T changes in 8.0% of the referees. Heart rate-dependent left bundle branch block was detected in one patient, and decreased maximal aerobic capacity was found in another patient.

4.1.9 Correlations between body composition analysis results and fitness measurements

Considering body composition analysis results and fitness markers measured during the CPET examinations, positive correlations were found between relative $\dot{V}O2_{max}$ values and height ($r = 0.329$, $R^2 = 0.108$, $p = 0.001$) and FFMI ($r = 0.456$, $R^2 = 0.208$, $p < 0.001$), while negative correlation was revealed with body fat percentage ($r = -0.705$, $R^2 = 0.497$, $p < 0.001$). Correlating maximal ventilation with body composition analysis parameters, numerous relationships were found (height: $r = 0.718$, $R^2 = 0.516$, $p < 0.001$; weight: $r = 0.735$, $R^2 = 0.540$, $p < 0.001$; BMI: $r = 0.556$, $R^2 = 0.309$, $p < 0.001$; FFMI: $r = 0.734$, $R^2 = 0.539$, $p < 0.001$; body fat percentage: $r = -0.461$, $R^2 = 0.213$, $p < 0.001$).

4.1.10 Comparison of the first and second division referees

Compared to the first-division referees, second-division referees reached higher exercise time, maximal HR, and maximal ventilation values, with similar peak lactate and $\dot{V}O_{2max}$ values. The second-division referees also reached their anaerobic threshold later. Data are shown in *Table 3*. About 9.8% of the first-division referees and 14.3% of the second-division referees did not reach the estimated values of the general population in ventilation. In comparison, 2.0% of the first and 4.1% of the second-division referees did not reach the calculated values of the general population in oxygen uptake. However all results were within the physiological range.

4.1.11 Additional examinations

Holter ECG recordings were carried out in seven cases; a significant number of PVCs was found in two cases (PVC: 9.4% and PVC: 1.6%), and one out of these patients also had significant ventricular bigeminy episodes as well as ventricular triplets (*Figure 9.*). In total, ten ambulatory blood pressure monitoring examinations were indicated. Normal blood pressure values were measured in three cases, new onset hypertension was diagnosed in two cases, undertreated hypertension in one case, and slightly elevated blood pressure values in two cases; all of these patients were male. Two patients did not undergo the examinations for their personal decisions.

All together 27 referees have undergone CMR due to offered screening in 12 cases and for diagnostic indications in 15 cases. Diagnostic CMR examinations were carried out because of personal history of syncope in one case, minor echocardiography changes in three cases (left ventricular hypertrophy: 1, interatrial septal aneurism: 1, enlarged right ventricular dimensions: 1), and resting or exercise ECG changes in 11 cases (frequent ventricular premature beats: 4, ST-T changes: 6, heart rate dependent left bundle branch block: 1). Hypertrabecularization was seen in two cases, borderline left and right ventricular functions in three cases — one out of them also had a wall motion abnormality. One case of aortic dilatation and bicuspid aortic valve, previously found with echocardiography, was confirmed by CMR. In the case of one referee, circular pericardial contrast enhancement referring to previous pericardial inflammation was detected. A CCT was carried out in four cases due to wall motion abnormality in one case and stress ECG ST-T abnormalities and PVCs in three cases. Non-significant coronary artery atherosclerosis was diagnosed in one case (*Figure 10.*), and LAD bridge was found in another. Two more patients with CCT indications have not undergone the examinations because of their personal decisions.

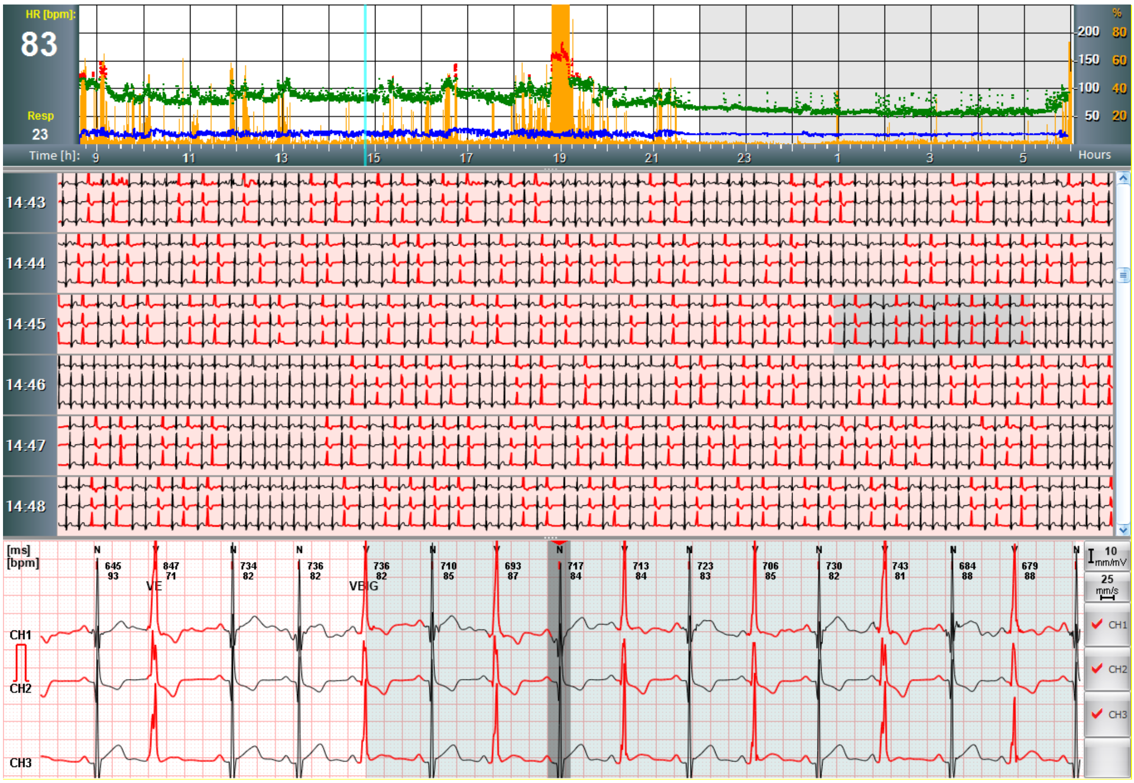

Figure 9. *Holter ECG recording of a 22-year-old asymptomatic male handball referee performed due to exercise induced single premature ventricular contractions. (96) Heart rate (normal: green, tachycardia: red), respiration rate (dark blue) and movements (orange) are shown against time at the top of the figure. The high number of premature ventricular contractions (red beats) is presented between normal beats (black) during a resting daytime period on the middle part of the picture. A representative section of the recording shows ventricular bigeminy at the bottom. The examination revealed 9.4% single monomorphic premature ventricular contractions, numerous episodes of ventricular bigeminy and ventricular triplets. Echocardiography and CMR examinations proved to be normal. Beta-blocker therapy was initialized, and regular cardiology follow-up was indicated. Abbreviations: CMR, cardiac magnetic resonance; HR, heart rate; Resp, respiration; N, normal beat; V, ventricular beat.*

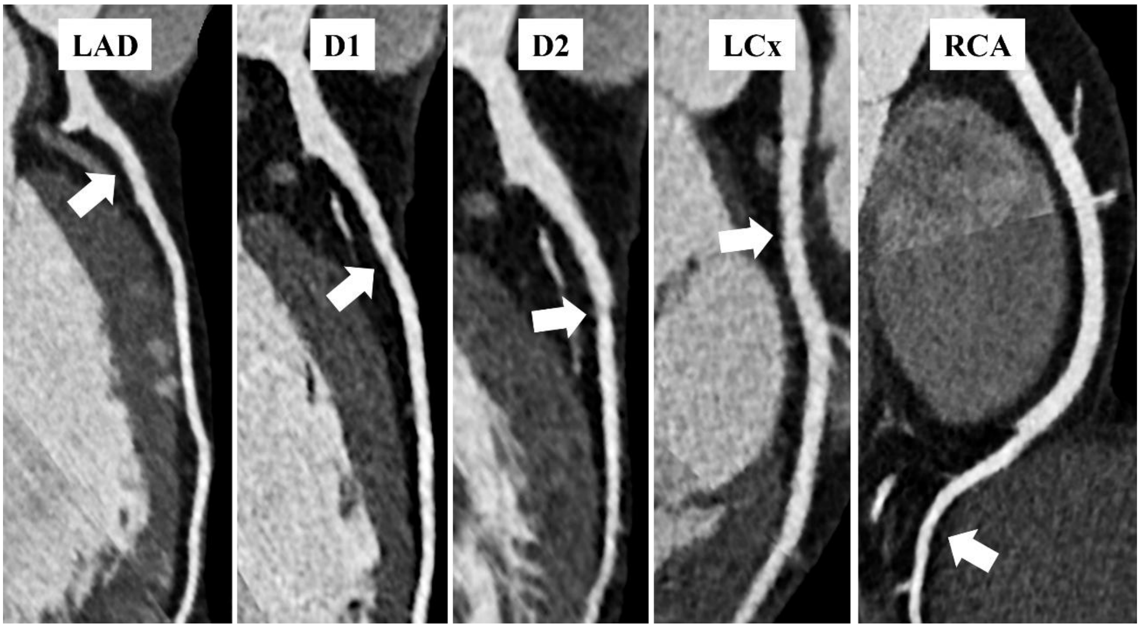

Figure 10. *CCT of a male referee with non-significant coronary artery atherosclerosis. (96) The CCT pictures of a 45-year-old asymptomatic male handball referee with no cardiovascular risk factors except for slightly elevated LDL cholesterol level. The examination was performed due to significant lateral ST-T changes recorded during exercise stress testing and revealed non-significant low-density non-calcified atherosclerotic plaques in all main coronary arteries (arrows). Statin therapy was initiated, and regular cardiology follow-up was indicated. Abbreviations: CCT, cardiac computer tomography; LAD, left anterior descending artery; D1, first diagonal artery; D2, second diagonal artery; LCx, left circumflex artery; RCA, right coronary artery.*

4.1.12 Interventions

Lifestyle changes were advised to 58.0% of the referees, including quitting smoking, losing weight, and introducing dietary changes (*Table 4.*). New antihypertensive drug therapy was offered in 2 cases, antihypertensive drug therapy modification in 1 case, and regular blood pressure monitorization in 12 cases. Lipid-lowering therapy was started in three male patients because of elevated lipid levels in all cases and also a non-significant coronary artery disease in one case. Beta-blocker therapy was initialized in one patient for the treatment of frequent PVCs. Oral iron supplementary therapies and control blood testing were suggested in 22.0% (male: 9.0%). Regular cardiology control examinations were recommended for 29 patients. Recommendation of lifestyle changes was more often in male referees, and iron supplementation was suggested in more female referees. No difference was found between former elite and former non-elite referees regarding the number of interventions indicated.

Table 4. *Number of interventions indicated by the extended cardiology screening of handball referees.*

Categorical variables are reported as number and frequencies (%).

Interventions	Male (n=64)	Female (n=36)
Lifestyle changes	42 (65.6)	16 (44.4)
Stopping smoking	15 (23.4)	6 (16.7)
Losing weight	12 (18.8)	1 (2.8)
Dietary advice	37 (57.8)	11 (30.6)
Oral iron supplementation	9 (14.0)	13 (36.1)
Antihypertensive drug therapy (new or modified)	3 (4.7)	0 (0)
Lipid lowering drug therapy	3 (4.7)	0 (0)
Rhythm control drug therapy	1 (1.7)	0 (0)
Cardiology follow-up	20 (31.3)	9 (25.0)

4.2 Long-term effects of a SARS-CoV-2 infection on sport performance and physical fitness of elite athletes

Cardiology control measurements after returning to high-intensity training following SARS-CoV-2 infection were performed in asymptomatic elite athletes, symptomatic athletes and athletes with pathological findings.

4.2.1 Results of asymptomatic elite athletes

The analysis was performed on 165 asymptomatic elite athletes (male: 122 (73.9%), age: 20 years (IQR: 17–24 years), training: 16 hours/week (IQR: 12–20 h/week)) from various types of sport (*Figure 11*). The examinations were performed 93.5 days (IQR: 66.8–130.0

days) following the first signs of a verified SARS-CoV-2 infection, including 21 days (IQR: 14–28 days) of training cessation and after achieving maximal training intensity.

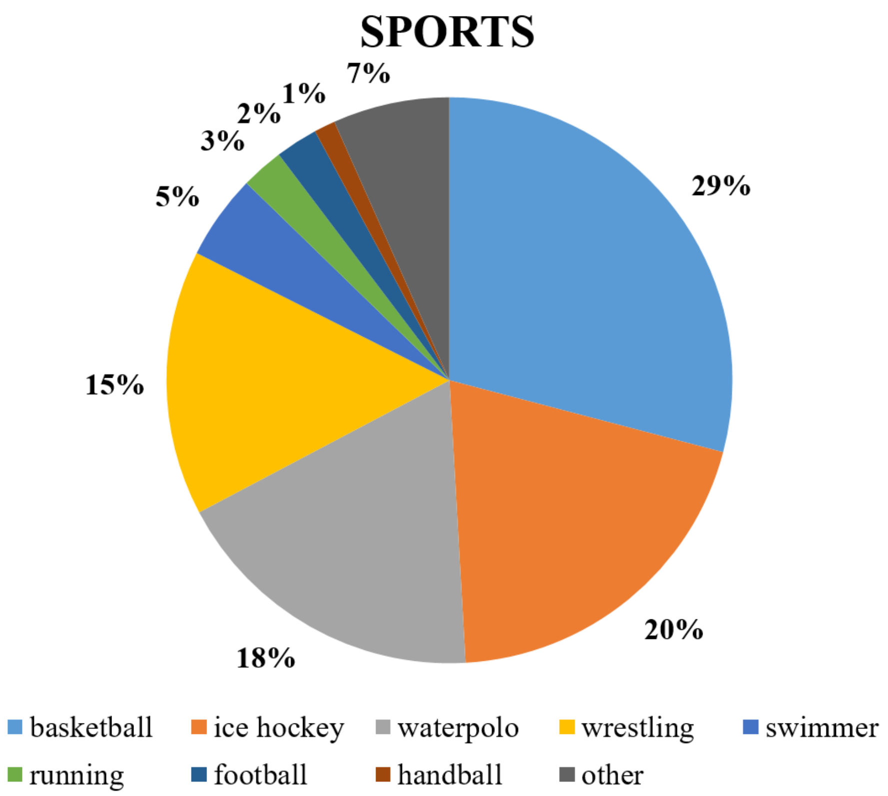

Figure 11. Types of sports of the examined asymptomatic elite athletes after SARS-CoV-2 infection

During the acute phase, 28 (17.0%) athletes had an asymptomatic infection, 136 (82.4%) had mild symptoms, while 1 (0.6%) athlete had moderate symptoms due to the SARS-CoV-2 infection.

Slightly elevated high-sensitive Troponin T (hs Troponin T) levels were measured in one (0.6%) elite asymptomatic athlete. In this case, a slightly elevated hs Troponin T level (15 ng/L) was present four months after the SARS-CoV-2 infection, and all other laboratory blood measurements, echocardiography, and CPET examinations were negative. After skipping training for two weeks, hs Troponin T level normalized according to the control laboratory measurements. Therefore, the hs Troponin increase was considered sports-related in this case.

Control echocardiographic examinations proved slightly increased pulmonary pressure in two (1.2%) asymptomatic elite athletes (32 + 5 mmHg and 36 + 3 mmHg); no other supposedly COVID-19-related changes were measured. In these cases, chest x-ray examinations were carried out without any pathological results. Further controls performed 7–14 days later showed normal pulmonary pressure values, and no additional abnormalities were recognized. Further echocardiographic findings independent from SARS-CoV-2 infection were preserved left and right ventricular ejection fraction (n = 1, 0.6%), slight diastolic dysfunction (n = 1, 0.6%), Barlow type mitral valve with mitral annular disjunction (n = 1, 0.6%) and left ventricular hypertrabecularization (n = 2, 1.2%).

Most of the asymptomatic elite athletes had satisfactory fitness levels as per the results of CPET. (*Table 5.*) The resting heart rate was 70 BPM (IQR: 64–79 BPM). During CPET examinations, the athletes achieved a maximum heart rate of 187 BPM (IQR: 181–194.5 BPM) (94.7 ± 4.3% of the calculated maximal heart rate), a $\dot{V}O2_{max}$ of 50.9 ± 6.0 ml/kg/min, and a maximal ventilation of 143.7 ± 30.4 l/min. The athletes reached their anaerobic threshold at 87.0 ± 6.4% of their $\dot{V}O2_{max}$, with a heart rate of 93.2% (IQR: 90.7–95.3%) of their maximal values. The 1-min heart rate recovery was 27 BPM (IQR: 22–34 BPM).

4.2.2 Comparison of CPET results before and after a SARS-CoV-2 infection in elite athletes

In 62 athletes, previous CPET results from before the SARS-CoV-2 infection were also available (*Table 5.*). Follow-up time between CPET examinations before and after the infection was 0.74 years (IQR: 0.61–1.78 years). The CPET exercise time proved to be longer after the infection compared to the previous results (pre- vs. post-infection: 13.0 min (IQR: 11.0–15.0 min) vs. 14.0 (IQR: 12.0–15.8) min, $p = 0.003$). Regarding $\dot{V}O2_{max}$ and maximal ventilation, even higher values were observed after the infection as compared to the previous examinations. (*Figure 12.*) Moreover, comparing the pre- and post-infection examinations, the athletes achieved similar maximal blood lactate levels during the exercise tests and spent a similar percentage at the anaerobic phase. At the anaerobic threshold, a higher heart rate ratio to the maximal heart rate and a similar oxygen uptake ratio to the $\dot{V}O2_{max}$ were measured. (*Figure 13.*) Compared to the previous results, a slight decrease in maximal heart rate was observed on the CPET after the infection (*Table 5.*); however, results corrected for age showed no significant change in maximal heart rate (adjusted pre- vs. post-infection: 190.6 ± 12.5 vs. 188.2 ± 12.0 BPM, p = 0.086). No significant differences were observed between VE/VCO2 slopes before and after the infection. However, individual cases of decreased exercise capacity (more than 10% decrease of $\dot{V}O_{2max}$ at the post-COVID-19 CPET compared to the previous examinations) were also confirmed by the CPET results (N = 6 [9.7%]).

Table 5. *Cardiopulmonary exercise testing follow-up results of elite asymptomatic athletes after a SARS-CoV-2 infection. (97)*

All CPET following SARS-CoV-2 infection (N=165) and for comprehension the results before and after SARS-CoV-2 infection (N=62). Follow-up time after the onset of the first symptoms of SARS-CoV-2 infection was 93.5 days (IQR: 66.8 – 130.0 days). Time between the CPET examinations before and after SARS-CoV-2 infection: 0.7 years (IQR: 0.6 – 1.8 years). Continuous variables are presented as means ± SD or median (Q1-Q3) depending on the normality of the results. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HR_{rest}, resting heart rate; HR_{max}, maximal heart rate; HR_{AT}, heart rate at the anaerobic threshold; $HR_{recovery}$, first minute heart-rate recovery after exercise testing; $\dot{V}O_{2max}$, maximal oxygen uptake; $\dot{V}O_{2AT}$, oxygen uptake at the anaerobic threshold; VE, ventilation; Lac_{max}, maximal lactate value; AT, anaerobic threshold; FEV1, Forced Expiratory Volume in 1 Second; VE/VCO_2 slope, ventilatory efficiency slope. Italics indicates statistical significance between the before and after SARS-CoV-2 examinations.

CPET results after SARS-CoV-2 (N=165)	Parameters	CPET follow-up results (N=62) Before SARS-CoV-2	After SARS-CoV-2	p
70 (64–79)	HR_{rest} (BPM)	72 ± 14	69 ± 14	0.174
187 (181–195)	HR_{max} (BPM)	190 (183–200)	187 (181–196)	*0.024*
94.7 ± 4.3	HR_{max} (% of calculated max.)	95.6 ± 5.0	94.3 ± 4.4	0.077
173 (166–184)	HR_{AT} (BPM)	170 (163–179)	171 (166–179)	0.277
93.2 (90.7–95.3)	HR_{AT} (% of HR_{max})	90.6 (86.3–93.5)	91.4 (90.2–93.4)	*0.004*
27 (22–34)	$HR_{recovery}$ (BPM)	29 (22–35)	27 (21–34)	0.290

Table 5. (continued) *Cardiopulmonary exercise testing follow-up results of elite asymptomatic athletes after a SARS-CoV-2 infection. (97)*

CPET results after SARS-CoV-2 (N=165)	Parameters	CPET follow-up results (N=62) Before SARS-CoV-2	After SARS-CoV-2	p
50.9 ± 6.0	$\dot{V}O_{2max}$ (ml/kg/min)	49.9 ± 5.6	52.2 ± 5.6	*0.004*
44.2 ± 5.5	$\dot{V}O_{2AT}$ (ml/kg/min)	41.8 ± 4.5	44.2 ± 5.0	*<0.001*
87.0 ± 6.4	$\dot{V}O_{2AT}$(% of $\dot{V}O_{2max}$)	84.0 ± 7.4	85.1 ± 7.3	0.289
143.7 ± 30.4	VE (l/min)	146.9 ± 27.8	155.3 ± 29.2	*0.008*
8.1 (6.6–10.0)	Lac_{max} (mmol/l)	8.5 (7.0–11.1)	8.7 (6.8–10.6)	0.465
13.1 (11.0–15.0)	Exercise time (min)	13.0 (11.0–15.0)	14.0 (12.0–15.8)	*0.003*
9.2 ± 2.6	AT time (min)	8.5 ± 2.8	9.5 ± 2.8	*0.003*
69.0 (61.2–77.3)	AT time (% of all time)	62.7 ± 14.3	66.9 ± 13.6	0.113
100.8 ± 16.8	FEV1 (% of expected)	105.3 ± 14.7	107.1 ± 17.6	0.198
26.3 ± 3.0	VE/VCO_2 slope	26.2 (24.3–28.3)	25.7 (24.7–27.7)	0.713

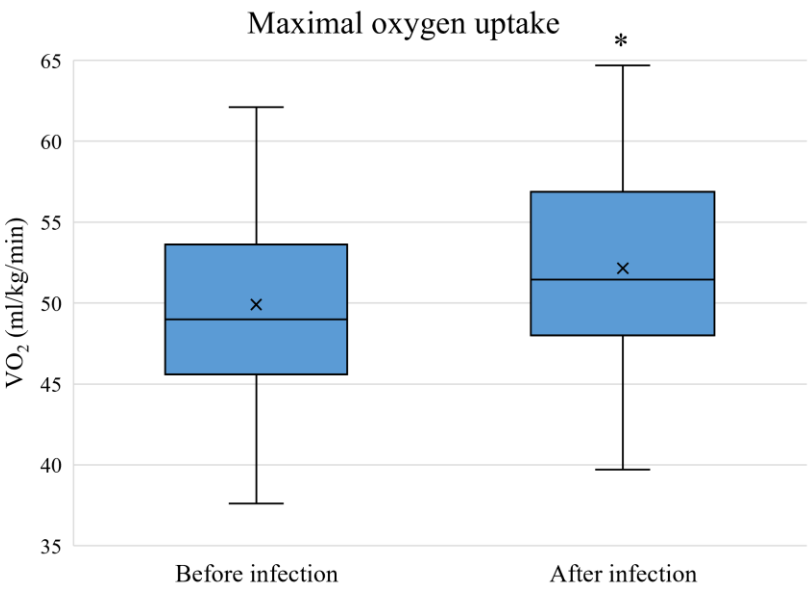

Figure 12. *Maximal oxygen uptake of the examined asymptomatic elite athletes before and after the SARS-CoV-2 infection (n = 62). (97) Abbreviations: VO2, oxygen uptake; *, p < 0.005.*

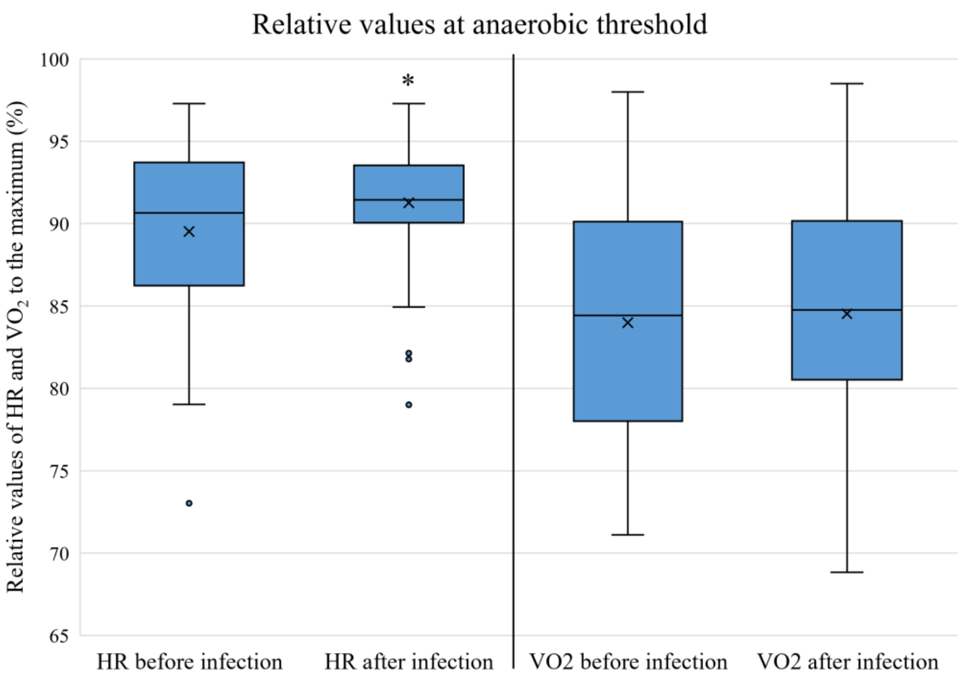

Figure 13. *Relative heart rate and oxygen uptake at the anaerobic threshold in relation to the maximal values of the examined asymptomatic elite athletes before and after the SARS-CoV-2 infection. (97) Abbreviations: HR, heart rate; VO2, oxygen uptake; *, p < 0.005.*

Detailed evaluation revealed resting or exercise-induced atrial or ventricular arrhythmias (single premature supraventricular beats, short supraventricular run, single premature ventricular beats or exercise-induced sustained ventricular tachycardia) or significant ST-T changes (ST-depression, T-wave inversion) in 8 (4.8%) athletes, while no pathological resting or exercise-induced corrected QT interval changes (calculated by the Bazett formula) were found in any of the athletes. In these cases, no direct connection between ECG abnormalities and the infection was proven, but further evaluation and close follow-up were recommended to exclude any potentially malignant arrhythmias or cardiac pathologies. (*Table 6.*) Behind the above arrhythmias, no structural cardiac abnormalities were revealed by the detailed cardiac evaluation. The exercise-induced sustained ventricular tachycardia proved to be a Belhassen-type arrhythmia. Regarding the ST-depression cases, one athlete (with 0.5-1 mm descending ST depression and T-wave inversion in inferior leads during the CPET) had non-significant ischemic heart disease, while another one (with transient 0.5-1 mm horizontal ST depression and biphasic T-waves in V5-V6 leads during CPET) had a coronary artery bridge due to the results of cardiac CT examinations. By hypertensive exercise blood pressure responses and ambulatory blood pressure monitoring results, a new initiation of antihypertensive therapy was necessary in 7 cases. (*Table 6.*).

In 22 (13.3%) asymptomatic elite athletes, only the echocardiography (n = 7, 4.2%) or CPET examinations (n = 15, 9.1%) revealed cardiovascular pathologies requiring treatment or follow-up. In cases of cardiac pathologies, further examinations, restrictions in sports activity, and follow-up were recommended according to the current European guidelines.

Table 6. *Clinical findings of basic, cardiopulmonary exercise testing and further examinations and treatments among 165 asymptomatic elite athletes 93.5 days (IQR: 66.8 – 130.0 days) after SARS-CoV-2 infection. (97)*

Abbreviations: MAD, mitral annular disjunction; CPET, cardiopulmonary exercise testing; VPB, ventricular premature beats; VT ventricular tachycardia, SVPB, supraventricular premature beats; SV, supraventricular; STD, ST-segment depression; FEV1, forced expiratory volume during the first second; CT, computer tomography

Clinical findings of asymptomatic elite athletes (N=165)	N	%
Laboratory test findings		
slightly increased high-sensitive Troponin T	1	0.6
Echocardiographic findings		
preserved left/right ventricular ejection fraction	1	0.6
slightly increased pulmonary artery pressure	2	1.2
diastolic dysfunction Grade I.	1	0.6
Barlow type mitral valve + MAD	1	0.6
left ventricular hypertrabecularization	2	1.2
CPET findings		
exercise induced VPB	4	2.4
exercise induced VT	1	0.6
exercise induced SVPB	1	0.6
exercise induced SV runs	1	0.6
exercise induced STD	3	1.8
decreased FEV1	1	0.6
Holter ECG findings		
significant VPB %	1	0.6
SV runs	1	0.6
Cardiac CT findings		
non-significant ischaemic heart disease	1	0.6
coronary artery bridge	1	0.6
Treatments		
new antihypertensive therapy	7	4.2

4.2.3 Results of athletes with pathological findings or ongoing symptoms during the visit

The results of those elite and non-elite athletes who still had symptoms or had positive clinical findings during the visit (n = 18, elite athlete: n = 9) were evaluated separately and are detailed below.

At the time of the control measurements, 11 athletes were still symptomatic (elite athletes: n = 5), although previously all of them only had mild symptoms in the acute phase of the infection. Symptoms were decreased exercise capacity (n = 4), palpitations (n = 3), exercise-induced shortness of breath (n = 2), worsening symptoms of asthma bronchiale (n = 2), or peripheral skin symptoms (n = 1). (*Table 7.*).

One athlete, who had mild acute symptoms for 12 days due to the COVID-19 disease previously, suffered from a long-standing mild, stabbing chest pain starting almost two weeks after the onset of the first symptoms and visited our Clinic for the first time two months after the starting signs of the disease. Due to these late symptoms, a CMR examination was carried out and revealed preserved left and right ventricular ejection fractions, and inferolateral and apical-lateral sub-epicardial late gadolinium enhancement without oedema as a potential sign of previous myocarditis. A follow-up CMR carried out eight months later detected the regression of these pathological signs (late gadolinium enhancement area 2020.11.: 9% vs. 2021.07.: 5%). Due to the timing of the infection, the long-standing symptoms and in the absence of other infections, this case was considered as a previous COVID-19 myocarditis.

In an elite athlete who still had effort dyspnea symptoms, decreased exercise capacity was revealed. This athlete suffered from asthma bronchiale, diagnosed before the SARS-CoV-2 infection and treated with optimal medical therapy. However, the symptoms of asthma bronchiale worsened in the long term following the infection. As a consequence, a significant decrease was measured in the fitness status, comparing the CPET results before and after the infection (*Figure 14.*). After pulmonary examinations, asthma bronchiale treatment was optimized, and the symptoms of the athlete resolved.

Table 7. *Clinical findings of basic, cardiopulmonary exercise testing and further examinations and treatments among 18 athletes with previous positive results or ongoing symptoms during the second visit. (97)*

Abbreviations: CPET, cardiopulmonary exercise testing; VPB, ventricular premature beats; nsVT, non-sustained ventricular tachycardia; STD, ST-segment depression; AF, atrial fibrillation; CT, computer tomography; PCI, percutaneous coronary intervention

Clinical findings of athletes with ongoing symptoms or previous positive results (N=18)	N
Ongoing symptoms	
decreased exercise capacity	4
palpitations	3
exercise induced dyspnoea	2
worsening symptoms of asthma bronchiale	2
peripheral skin symptoms	1
Laboratory test findings	
slightly increased high-sensitive Troponin T	1
CPET findings	
exercise induced VPB	3
exercise induced nsVT	1
exercise induced STD	1
Holter ECG findings	
significant VPB %	2
paroxysmal AF	1
Cardiac CT findings	
anomalous coronary artery origin	1
non-significant ischaemic heart disease	1
Treatments	
right coronary artery PCI	1

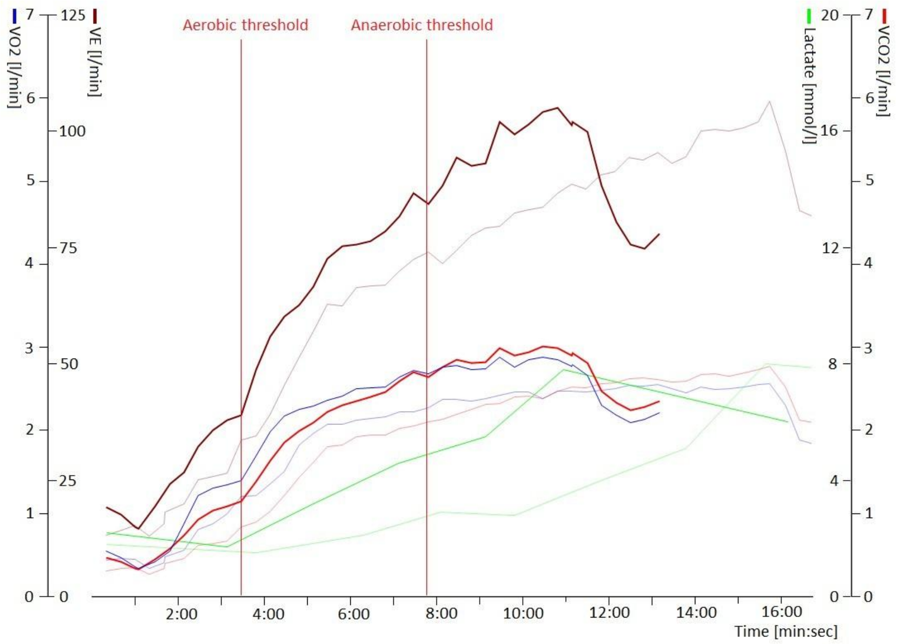

Figure 14. *Decreased exercise capacity of a 19-year-old female water polo player after SARS-CoV-2 infection. (97) On the graph, two CPET examinations are shown, between the two exanimations the follow-up time was 0.61 year. The earlier results of the examinations are shown with pale colours, the examinations after the SARS-CoV-2 are shown with sharp lines. The athlete achieved shorter running time on the same CPET protocol, with approximately the same ventilation (brown lines), slightly higher oxygen uptake (blue lines) and carbon dioxide production (red lines), worse metabolic adaptation to sports activity, which is represented by the increased lactate levels (green lines). The aerobic and anaerobic thresholds are represented with two vertical lines during the post-infection examination. Further examinations revealed the worsening of her previously known asthma bronchiale symptoms and her treatment was optimized. Abbreviations: VO2, oxygen uptake; VE, ventilation; VCO2, carbon-dioxide production.*

In the case of a master athlete who had palpitations and fatigue after a moderate symptomatic SARS-CoV-2 infection, multiple PVCs, ventricular couplets, a short non-sustained ventricular tachycardia (5 beats), and multiple supraventricular premature beats were recorded on the CPET. Multiple polymorphic ventricular couplets and a 19-beat-long paroxysmal atrial fibrillation episode were recorded on the 24-hour Holter ECG. Due to the positive findings on the CPET and Holter ECG examinations and to the various cardiovascular risk factors, a CCT was carried out. A borderline significant stenosis was revealed on the proximal part of the right coronary artery. Dobutamine stress echocardiography was performed for further evaluation, but no ischaemic signs were revealed.

An asymptomatic non-elite master athlete with horizontal ST-depression in V4-V6 precordial leads proved to have anomalous right coronary artery origin and a significant pre-occlusive coronary artery disease. The right coronary artery originated from the left aortic sinus of Valsalva and turned immediately rightwards at a very acute angle and traversed between the pulmonary trunk and the aorta before returning to its ordinary course (*Figure 15.*). At the coronarography a 70-89% stenosis was revealed on the right coronary artery and a drug eluting stent was implanted.

In an asymptomatic case, elevated hs Troponin T levels were measured repeatedly starting from a previous visit 4 weeks following the SARS-CoV-2 infection, and similar values were measured during a more than 6-month follow-up (all hs Troponin T levels were between 40-50 ng/L). During this time, no symptoms appeared, and all examinations - including CMR - were negative. In this case, hs Troponin changes were considered an individual characteristic without cardiac diseases.

In cases of symptoms or cardiac pathologies, further examinations, restrictions in sports activity, and follow-up were recommended according to the current European guidelines.

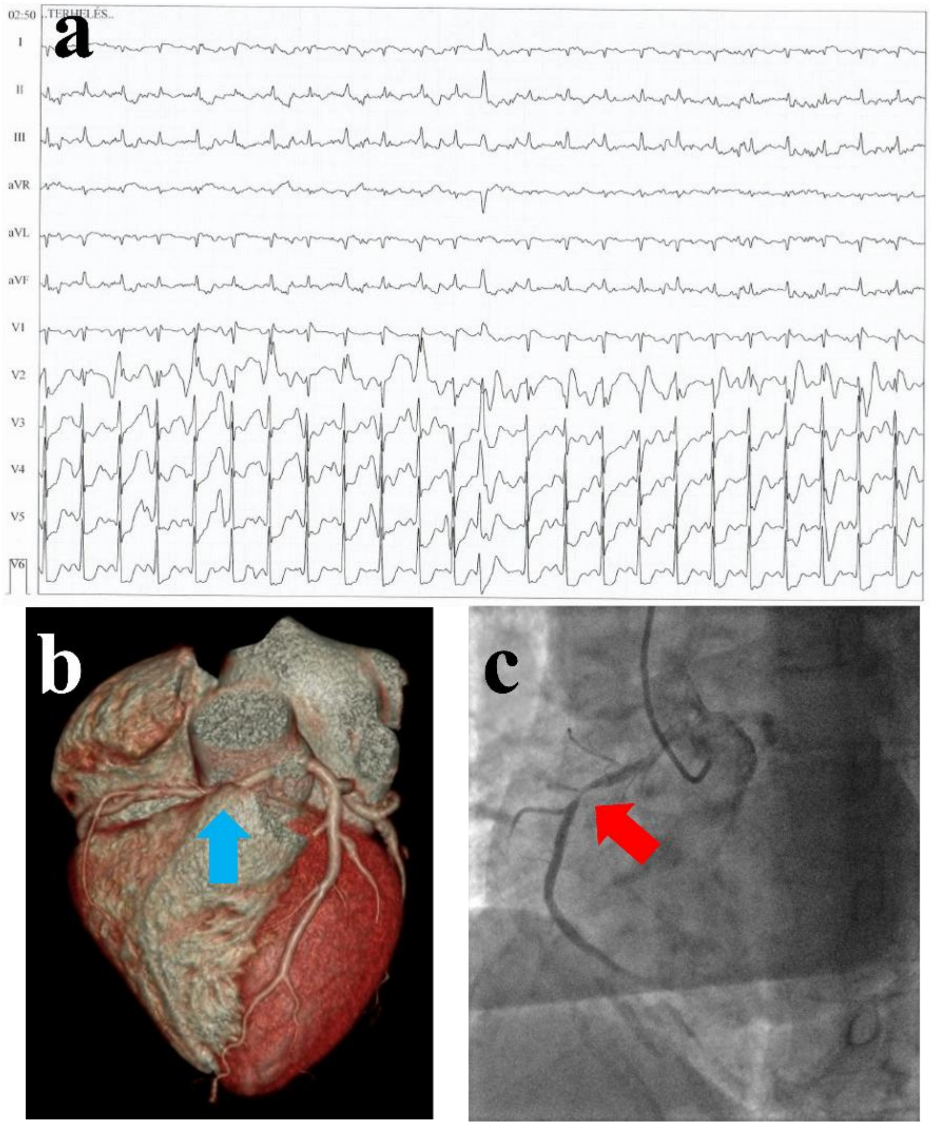

Figure 15. *The case of a 60-year-old female amateur runner, with non-COVID-19-related findings. (97) She had treated hypertension, the SARS-CoV-2 caused mild symptoms, and she still suffered from weakness 3 months after the infection. During her second visit, he CPET examination revealed significant horizontal 2 mm ST-depression in V4-V6 (panel A). The patient was referred to cardiac CT, where anomalous origin of the right coronary artery with a significant atherosclerosis was revealed (panel B). Due to these findings, a percutaneous coronary intervention was recommended, and a drug-eluting stent implantation was carried out (panel C). A dobutamine stress echocardiography was also performed after the intervention, where no ischemic regions, or wall motion abnormality were detected. The asymptomatic patient was advised to perform light-to-moderate intensity sport activities.*

5 Discussion

Our studies highlighted the importance of the extended examinations in underrepresented athlete populations, spanning from elite handball referees to athletes recovering from COVID-19. In our examinations, we pioneered comprehensive cardiovascular screening and physical fitness examinations in asymptomatic elite handball referees and also investigated long-term cardiac effects in athletes recovering from SARS-CoV-2 infection. These studies collectively advance our knowledge in sports cardiology, particularly regarding cardiovascular risk assessment, screening protocols, and return-to-sport guidelines in specialized athletic populations.

5.1 Importance of cardiovascular screening in special athletic populations

5.1.1 Resting examinations of handball referees

The extended screening of 100 Hungarian elite handball referees revealed alarming rates of cardiovascular risk factors that fundamentally challenge assumptions about the health status of sports officials.

The documentation of positive personal or family cardiovascular history in 24% of handball referees, combined with smoking rates of 21%, establishes a concerning risk profile. These smoking rates fall within the range reported for other sports officials, with O'Riordan et al. finding 35% smoking rates among Irish Gaelic athletic sports referees, while Tereshchenko et al. reported lower rates of 13% in professional Ukrainian football referees. (98, 99) However, our finding that former elite handball players tended to have higher smoking rates (25.6% versus 18.0%) suggests that past athletic achievements do not necessarily translate to sustained health-conscious behaviours. Identifying the reasons behind this and finding solutions is also an important task of sports medicine for the future.

Based on the guideline in force at the time, we identified elevated resting blood pressure in 38% of handball referees where immediate treatment was necessary in 6%. Analysing the data according to the actual guideline only 4% the referees had non-elevated blood pressure, while 58% had elevated and 38% had hypertension. (100) The identification of elevated resting blood pressure in a high percentage of handball referees contrasts markedly with findings from other sports officials. Bizzini et al. reported treated hypertension in only 1.1% of male FIFA football referees, with exercise hypertension occurring in 5.6%. (101) Similarly, Tereshchenko et al. found arterial hypertension in 10.2% of professional Ukrainian football referees. (99) The difference between these studies and our measurements could come from the different guidelines over time.

Physiological, sport-related changes in a large proportion of the referees, referring to regular training, were identified on the resting 12-lead ECG. Isolated grey zone changes requiring no further evaluations occurred in one-sixth of the referees. In terms of pathological ECG changes, T-wave inversion or biphasic T-waves in 6% were the most frequent abnormalities. These results correlate with the findings in both female and male FIFA football referees: physiological sport-related changes were common in both studies. (101, 102) Among the female football referees, no pathological ECG changes was found, while T-wave inversion was recorded in 4.4% among the male referees. Out of our nine patients having pathological resting ECG abnormalities, one was diagnosed with significant PVC number, one with pericardial contrast enhancement on the CMR, and one with hypertension, while in case of the other six referees (4 having ST-T abnormalities, 2 having resting sinus tachycardia) no cardiovascular pathologies could be explored behind the resting ECG changes.

Regarding the results of bioimpedance body composition analysis, prevalence of overweight (10%) and obesity (3%) was also remarkably high in our handball referee group. With just measuring the BMI 44% of the referees would be considered as overweight or obese, out of whom 70% had just fat-free mass increase without higher fat percentage. However, our results were more favourable compared to some international referee populations. O'Riordan et al. reported remarkable rates of 60.1% overweight and 25.7% obesity among Irish Gaelic athletic sports referees, while Brazilian football referees showed 44% overweight based on BMI and adipometer measurements. (98, 103) These comparisons suggest that handball referees maintain better body composition than some other sports officials, though still showing room for improvement.

By the results of the laboratory tests, our finding that a high percentage: 41% of the referees presented with dyslipidaemia represents a prevalence rate notably higher than the 32% typically observed in Olympic athletes, where dyslipidaemia has been identified as the most common cardiovascular risk factor globally. The results of the Olympic athletes also showed a lower rate in smoking compared to our referee population. (104)

Comparing the risk profile of the referee population, it resembles to professional rugby players, where elevated C-reactive protein was the most prevalent risk factor, followed by hypertension and dyslipidaemia. (105) This percentage of dyslipidaemia of the handball referees is very high compared to the results of male FIFA football referees (2.2% elevated serum lipid levels), although we do not know the exact cut-off values for that study. (101) Otherwise, a similar 37.5% of Brazilian football referees presented dyslipidaemia, and they had a higher average of total lipid levels compared to our population with nearly the same HDL cholesterol levels. (103)

The identification of iron deficiency in 22% of handball referees is surprisingly high and contrasts with findings from other referee populations. Bizzini et al. found only 2.2% mild anemia in male FIFA referees. (101) The difference between the two studies could come from the different gender composition, since most of the referees who had iron deficiency were female in our study. Since the anaemias revealed in our study were slight and the referees did not report any symptoms which could be caused by these changes, dietary deviation was assumed, oral iron supplementation was indicated, and control blood tests were recommended.

Comparing our results from the examinations of handball referees with a slightly older age group of the general population of Hungary based on the Budakalász study, we found lower BMI and lower rates of dyslipidaemia in handball referees. Moreover, the rate of smokers was slightly lower in our referee population comparing to the general population. (106) Altogether, the above results refer to the long-term positive effects of sport activity on health. However, we measured similar systolic blood pressure and even slightly higher mean diastolic blood pressure in the referee group, which is still higher than normal regarding the current guidelines. (100) As elevated blood pressure is a common problem also in elite athletes, further examinations are fundamental regarding the specific effects of different sport activities on the long-term trends in blood pressure. Revealing the potential pathophysiological effects of physical activity on blood pressure is substantial.

Echocardiographic examinations showed an average of 59.9 ± 3.3% left ventricular ejection fraction with normal average posterior end-diastolic- and intraventricular septal wall thicknesses on average. In our examinations, grey zone wall thickness was found in 2.0% at the posterior wall and in 3.0% at the septal wall. In our population, the most common pathological echocardiographic changes were first-grade mitral valve regurgitation in 6.0% and mitral prolapse syndrome in 3.0%. Other pathologies were rare, including single cases of interatrial septal aneurysm and hypertrabecularization, enlarged right ventricle dimensions in one referee, dilatation of the aortic root in two patients, with bicuspid aortic valve in one out of these. On the whole, typical signs of athlete's heart could not be seen in most of the referees.

In comparison, Caballero et al. described higher ejection fraction and thicker posterior end-diastolic wall and septal wall parameters (68.7 ± 8.9%, 9.5 ± 1.6 mm, 9.77 ± 1.5 mm, respectively) although they did not measure more than 12 mm at either wall in Spanish football referees. (107) Keller et al. measured higher left ventricular ejection fraction with thinner posterior and septal end-diastolic wall in female FIFA football referees (67.6 ± 4.2%, 8.3 ± 1.0 mm, 7.9 ± 1.0 mm, respectively). (102) Among female FIFA referees, the most common echocardiographic changes were mitral valve regurgitation in 17.6%, other changes were rare, such as aortic regurgitation in 2.0% and ventricular septal defect in 3.9%. (102) In male FIFA referees, the rate of valvulopathies was lower, mitral regurgitation was detected in 2.2%, mitral prolapse syndrome in 1.1%, while both dilatation of the aortic root and left ventricular hypertrabeculation were detected in 2.2% in this population. (101)

The most profound implication of our handball referee investigation lies in demonstrating that nearly half of the identified cardiovascular conditions did not cause physical signs or symptoms. This finding is in line with international research showing that elite athletes can harbour significant cardiovascular pathology despite apparent health. The Italian Olympic screening program of elite athletes of age 26.7 ± 4.3 years for male and 25.3 ± 4.1 years for female, identified potential sudden cardiac death risks in 4 of 772 athletes (0.5%) , requiring withdrawal from competitive sport. (108) The underlying conditions were arrhythmogenic cardiomyopathy in two cases, left ventricular non-compaction in one case and in one athlete with accessory conduction pathway with focal atrial tachyarrhythmias and recurrent fast supraventricular tachycardia. These findings underline the importance of extended cardiology screening programmes like ours in endangered athlete populations.

5.1.2 Resting examinations of post-COVID-19 athletes

Among the examined 165 elite athletes following SARS-CoV-2 infection, a great majority of the athletes had mild symptoms due to the infection in the acute phase while they were asymptomatic at the time of the examinations carried out after an average of 3 months following the infection. Additional 18 athletes who still had symptoms or had positive findings were also examined 3 months after the COVID-19. Out of the above, 174 elite athletes were examined with 2.8% still having COVID-19-related symptoms. These symptoms were decreased exercise capacity (n=1), exercise-induced shortness of breath (n=2) or worsening symptoms of asthma bronchiale (n=2).

The rate of long-term symptomatic athletes examined in our study was similar with other studies conducted on elite athletes. (109) The low percentage of symptomatic elite athletes in our study suggests no connection between training after the mandatory releasing tests and long-standing symptoms. As the incidence of these long-standing post-COVID-19 symptoms decrease with the elapsed time after the breakout of the disease, the ratio of remaining symptoms was, not surprisingly, much higher (18%) in a study examining an elite athlete group less than 3 weeks after the infection. (110)

Among those elite athletes who were asymptomatic at the time of the CPET examinations, 18 had minor complains during the first basic screening (tiredness: 7, mild atypical chest pain: 7, higher heart rate: 3, palpitation: 2, coughing: 1). All of these symptoms resoled at the time of the CPET examinations. In two asymptomatic athletes, elevated hs Troponin T levels proved to be individual or sports-related after thorough investigation.

The echocardiographic examinations revealed preserved left and right ventricular ejection fractions in 0.6%, slight diastolic dysfunction in 0.6%, Barlow type mitral valve with mitral annular disjunction in 0.6%, left ventricular hypertrabecularisation in 1.2% and slightly elevated pulmonary pressure in 1.2%. Due to the possible connection to the COVID-19 in cases of elevated pulmonary pressure, immediate chest X-ray examinations were also carried out showing negative results. Follow-up echocardiographies were also performed in 7-14 days, which showed normal pulmonary pressure values.

In our study, no new onset of inflammatory heart disease was revealed during the long-term follow-up period. However, one athlete appearing for the first examinations two months after the first symptoms of COVID-19 with long-standing chest pain, negative resting ECG, and dilated right ventricle and borderline left ventricular systolic function (ejection fraction: 50%) on the echocardiographic examination was sent to a CMR. By the results of the CMR, a supposedly SARS-CoV-2-related previous myocarditis was revealed.

Altogether, our results show that cardiac involvement after asymptomatic or mildly symptomatic SARS-CoV-2 infection in athletes is rare. These observations are in concordance with the results of a larger cohort study by Moulson et al. as well with the results of 147 highly trained athletes of Szabo et al. (111, 112) Systematic reviews summarizing data of long-term cardiac imaging manifestations also found low risk for myocardial or pericardial involvement after a SARS-CoV-2 infection. (113, 114) By examining 789 athletes, out of whom 58% had prior symptomatic COVID-19, Martinez et al. found that 0.6% had cardiac MRI findings suggesting inflammatory heart disease (115). In addition to these findings, they revealed changes in troponin levels (0.8%), ECG (1.3%) and echocardiography (2.5%) 19 days after SARS-CoV-2 infection. (115) These results are concordant with the work of Vágó et al., who did not find acute cardiac involvement among 12 young elite athletes shortly after the infection. (82)

5.2 CPET examinations in special athlete populations

The CPET examinations in sports sciences are primarily conducted among elite athletes for exercise physiology measurements and follow-up. However, these measurements could be informative for recreational athletes, for return-to-play protocols and for other athlete populations as well. In special athlete populations the CPET examinations would be also important for physical fitness evaluation and for the detection of cardiovascular pathologies. Collaborations with sports federations are important, as they could provide opportunities for a large number of athletes and sports professionals to undergo exercise testing.

5.2.1 Exercise-induced pathology detection in handball referees

The implementation of cardiopulmonary exercise testing revealed pathological changes in 16% of the referees with positive stress-ECG changes and 8% with elevated exercise blood pressure responses, findings that would have remained undetected through conventional resting evaluations. These rates exceed those reported in FIFA football referees, where Bizzini et al. found exercise-induced ST depression in 5.6% with no other exercise ECG changes detected. (101)

5.2.2 Exercise-induced pathology detection in post-COVID-19 athletes

The detailed screening and follow-up could help in the detection of supposedly SARS-CoV-2-related and unrelated alterations as well. Extending the routine screening with CPET examination in elite asymptomatic athletes revealed additional cardiovascular pathologies in 15 (9.1%) athletes.

Although no direct connection with the infection could be proven, detailed evaluation revealed exercise-induced atrial or ventricular arrhythmias or hypertension in some athletes. Although no structural abnormality was revealed in the back, these athletes needed special attention and close follow-up. In the symptomatic athlete group, a much higher 6 (33%) of the CPET examinations carried out positive findings, like shortness of breath due to worsening symptoms of asthma bronchiale, ventricular arrhythmias or exercise induced ST-segment depression. Behind the pathological ECG abnormalities, significant cardiovascular pathologies were revealed as anomalous coronary artery origin in 1 case and ischemic heart disease in another case. Since these diseases are not connected to COVID-19, these should be considered as side-findings.

5.2.3 Physical fitness evaluation of handball referees

By our results, the examined referees had a satisfactory fitness status compared to previous data regarding athletes who do mixed sports. (116, 117) According to our results, the measured oxygen uptake and ventilation values surpassed the estimated non-athlete reference values specified by the manufacturer in most of the cases. However, great individual differences were found in weekly training time, treadmill exercise time, aerobic capacity and anaerobic threshold time. These results highlight the necessity of routine physical fitness measurements, individual training programs, and reconsideration of minimal standards mandatory to be met regarding the elite handball referees.

As comparing male and female referees, females achieved similar treadmill exercise times as males, which is, although surprising, a welcome result, since they work in the same leagues. Regarding the results of the subgroup analysis, surprisingly, the referees from the second division achieved longer CPET examination times, anaerobic threshold times, and lower maximal ventilations. These results, as well as their higher maximal exercise HR, can be partially explained with their younger age.

According to previous literature data, handball referees perform at moderate intensity for most of the time during handball matches; however, in 3.6% of the game, they are exposed to heavy or severe load. (10) During these periods, they still need to be able to concentrate at maximum level. All the above underline the fact that referees need to prepare for the games with good physical condition, however, they perform trainings approximately 4 hours/week, while elite players train 10–20 hours/week. (118) Comparing the results of this study with a report on 291 male elite German handball players, we can state that our referee group had lower maximal aerobic capacity and similar peak lactate levels. (119)

In a Croatian study, no differences in maximal and average HR in referees between the two halves of a handball game were revealed. (120) These data support the fact that referees need to have a good long-lasting aerobic fitness level to referee the matches. Comparing the results of our younger referee population with the values of a small group of Brazilian handball referees, the maximal HR of referees was similar, while the maximal aerobic capacity proved to be lower in our study. (10) Moreover, comparing our results with the results of an older basketball referee population from Australia, the $\dot{V}O_{2max}$ was lower in our population. (121) The above-mentioned differences in maximal aerobic capacity can be explained by the fact that the other workgroups only used estimations to calculate the maximal aerobic capacity, while our team measured it directly by breath-by-breath measurement. Oxygen uptake results of 31 Croatian Premier Handball League referees are available, where the authors found that the $\dot{V}O_{2max}$ of them were 45.4 ± 6.1 ml/min/kg in an older population. (122) Their results were similar to our measurements for both first and second divisional Hungarian handball referees, despite the difference in age. No further literature data is available regarding breath-by-breath CPET analysis of the physical fitness of elite handball referees. In an Iranian study the authors found higher $\dot{V}O_{2max}$ (59.9 ± 7.1 ml/kg/min) values among elite football referees. (123) The differences in the results of the referees among the different type pf sports could be due to the specific sports loads.

In our referee population, huge personal differences could be observed in the fitness status. We found a great difference between the referees with the best and the worst $\dot{V}O_{2max}$ values, which could mean that some of them could meet the criteria to maintain a high-quality refereeing during the whole game, while those who achieved worse results during testing could have difficulties with their physical status during the games. However, better fitness status was not attached to refereeing in a higher division, possibly because previous experience and routine highly influenced their assignments. In 3 cases the referees did not reach the calculated values of the general population in oxygen uptake, but their results were still within the physiological range.

5.2.4 Physical fitness evaluation of post-COVID-19 athletes

Our study was carried out on a mixed group of athletes most of whom were asymptomatic or had mild-to-moderate symptoms during the COVID-19 infection. Referring to previous literature data and also our previous results, average $\dot{V}O_{2max}$ of the examined mainly mixed sport activity team of elite asymptomatic athlete population proved to be satisfactory 3 months after the infection. (124)

In a subgroup of asymptomatic elite athletes who also had previous CPET data from before the SARS-CoV-2 infection, except for a few cases, no significant decrease in $\dot{V}O_{2max}$ could be observed, but a significant increase in mean exercise time, $\dot{V}O_{2max}$, ventilation, and heart rate at the anaerobic threshold could be measured. These results could be explained with the fast recovery of the athletes as well as the intensive trainings before world competitions like the Olympic Games held in 2021. Different training phases at the time of the CPET measurements before and after the SARS-CoV-2 infection could also affect these results. In our study, no changes in FEV1, VE/VCO2 or VE/VCO2 slope were measured due to the COVID-19 infection in asymptomatic elite athletes. Cavigli et al. found similar VE/VCO2 slope results in athletes after suffering a SARS-CoV-2 infection. (125) Also their data support our results, as they did not find deviations on the resting spirometry in 90 asymptomatic or mildly symptomatic young athletes 30 days after recovering from a SARS-CoV-2 infection and compared to a healthy athlete group. Moreover, the authors did not find limitations of cardiac or pulmonary functions during CPET shortly after the infection. (125) Komici et al. also did not find a decrease in CPET parameters after COVID-19 in a short-term follow-up after the infection, however, in contrast to our results, they found a decrease in the FEV1. (126) The difference could be the time elapsed after the beginning of the infections; since in our study the average time between the infection and the examinations was around 3 months, while in the previously mentioned research it was necessary to be less than 30 days.

In contrast, in a football team cohort study of 30 athletes with (n = 18) and without (n = 12) previous SARS-CoV-2 infections were compared to each other and to their own previous values via spirometry and exercise stress ECG–performed 15 days after complete recovery. Compared to the previous personal measurements, a significant decrease was found in the SARS-CoV-2-infected group, however the SARS-CoV-2-negative athletes also suffered the same amount of detraining. Not surprisingly, these data suggested that COVID-19 infection could cause a significant decrease in fitness around 1 month after the onset of the disease, which exceeded the predicted decrease from detraining. (127) Unfortunately, CPET values for this group are not available. Moreover, these results underline that restarting maximal intensity exercise 2 weeks after complete recovery is not recommended, the step-by step increase of training intensity and amount is more favourable. Csulak et al., who examined 46 professional swimmers out of whom 14 were SARS-CoV-2-infected, did not find major differences in CPET results before (measured in 2019) and after (measured in 2021) the infection. (128)

Among 16 male elite volleyball players after mild SARS-CoV-2 infection with 22 days of training cessation followed by 20 days of training before the CPET, a Serbian workgroup found good aerobic fitness levels (VO_{2max}: 44.1 ± 3.4 ml/kg/min; ventilation: 152.4 ± 18.7 l/min; HR_{max}: 183.0 ± 8.3 BPM). (129) They indicated that the infection had no additional effects on any athletes to the detraining period, which was generally true about our study group as well, with a few exceptions, where a decrease could be observed in the fitness values. (129) In our athlete group, no significant decrease, but increase was found in some parameters of the CPET, which could be explained by the longer follow-up time after the infection, thus more time was allowed for rehabilitation and achieving maximal intensity trainings.

The initial MRI results showed an overwhelming proportion of cardiac involvement after SARS-CoV-2 infection, but further results presented a lower rate of cardiac involvement. (82, 130) Researchers from the Netherlands followed a cohort of 259 elite athletes, of whom 47,5% were infected, for up to 27 months and found that while four athletes showed late gadolinium enhancement on CMR, none required career cessation, supporting the overall safety of return-to-sport protocols. (131) Among 147 highly trained athletes, Szabó et al. performed CMR and a modest frequency of cardiac involvement was revealed (4.7%), with definitive signs of myocarditis only in 1.4%. (112)

Also identifying athletes for long-COVID syndromes is important to help with return-to-play. (132) In our cohort some athletes with long-COVID or worsening of previously known asthma bronchiale were detected and individual recommendations were advised.

5.3 Limitations

Our studies were conducted on relatively large populations; however, all were single-centre investigations. This design may limit the generalizability of our findings. Multicentre and international studies would be needed to broaden the applicability of our results to other athletic populations.

A limitation of our handball referee study is the lack of direct comparison between referees and the elite handball players whose matches they officiate, as well as with international handball referees of similar quality. Such comparisons could provide deeper insights into the specific physical and performance demands placed on elite referees in relation to both the athletes they oversee and their peer group. Also a non-athlete control group would be favourable to be included to examine the incidence rates of the cardiovascular pathologies and to evaluate their fitness levels.

In the post-COVID-19 athlete cohort, the sample size could be expanded and stratified according to the different SARS-CoV-2 variants, which may have distinct effects on cardiovascular health. Additionally, pre-infection CPET data were obtained retrospectively, and athletes were in different phases of their training cycles at the time of these assessments. Ideally, CPET examinations should be performed at comparable training phases to ensure more accurate longitudinal comparisons. Comparison with a sedentary control group could help us to examine the SARS-CoV-2 response in non-athletes and help to identify differences with the response of elite athlete to the infection. Finally, our follow-up period was limited to three months post-infection. Longer-term follow-up studies are necessary to fully evaluate the enduring impact of SARS-CoV-2 infection on athletic performance and fitness status, although our current results suggest no significant decline in most athletes within the three-month period.

6 Conclusions

Our investigations fundamentally reshape our understanding of cardiovascular health in special athletic populations by demonstrating that comprehensive screening can identify substantial hidden pathologies either with immediate clinical implications or long-term negative cardiovascular effects. The finding that nearly half of cardiovascular conditions in handball referees would remain undetected through conventional mandatory screening, combined with the identification of serious cardiac pathologies in some post-COVID athletes, establishes compelling evidence for expanded cardiovascular assessment protocols in sports medicine. The high prevalence of risk factors in handball referees demonstrates that athletic participation whether as competitors or officials, does not confer immunity from cardiovascular disease, and may create unique risk profiles requiring specialized evaluation approaches. Our examinations of athletes after SARS-CoV-2 infection as a part of worldwide athletic screening never seen before also highlight the importance of widely implemented extended cardiology. Although long-term pathological effects of COVID-19 proved to be rare due to our results, other severe pathologies not connected to the infection were also revealed. These results are in line with research showing that even Olympic athletes can have significant cardiovascular risk factors. Studies of professional athletes across various sports have consistently identified substantial prevalence of hypertension, dyslipidaemia, and other modifiable risk factors

Regarding physical fitness, our data underline the great individual differences among elite Hungarian handball referees, as well as the remarkable differences in the amount of training regularly done by them. Therefore, although refereeing experience highly affects the quality of refereeing, individual training plans should be prescribed for referees to reduce the differences observed in their physical fitness levels.

The success of comprehensive screening in handball referees and post-COVID athletes suggests similar approaches may benefit other athletic populations. International evidence supports expanding screening programs, with research from multiple countries demonstrating that systematic cardiovascular evaluation can identify significant pathology in apparently healthy athletic populations. (108, 133, 134) However, significant variability exists in screening protocols, with only a minority of organizations including echocardiography and stress testing as standard practice. (133, 135) We recommend that these extended examinations be performed regularly, or at minimum following infections (e.g. SARS-CoV-2 infection) in all elite athletes to reduce the risk of sudden cardiac death. Supplementing these tests with CPET measurements whenever possible provide additional information on cardiovascular health.

The clinical significance of our findings extends beyond individual patient care to encompass broader questions of sports safety, preparticipation screening adequacy, and resource allocation in preventive cardiology. When compared to international studies, these results consistently support the value of comprehensive screening while highlighting the unique cardiovascular challenges faced by different athletic populations. The integration of advanced diagnostic techniques with functional assessment provides a model for contemporary sports cardiology that balances diagnostic thoroughness with practical implementation considerations, ultimately serving to enhance both safety and performance in athletic populations.

7 Summary

Regular physical activity reduces cardiovascular disease risk and all-cause mortality, yet high-intensity exercise could be contraindicated in certain cardiovascular conditions. Limited data exists on cardiovascular screening and physical fitness of special athlete populations, including referees and post-infectious athletes. Our aim was to examine cardiovascular risk factors and fitness status of elite handball referees and post-COVID-19 athletes at the Heart and Vascular Center in a cross-sectional setup.

We evaluated the top 100 Hungarian handball referees, revealing prevalent risk factors, including dyslipidaemia (41%), elevated resting blood pressure (38%), and positive medical history (24%). Stress-ECG was positive in 19%, and imaging abnormalities found in 19%. Interventions included lifestyle modifications, antihypertensive or lipid-lowering therapy, and iron supplementation in many cases. These results emphasise that, despite athletic activity, multiple cardiovascular risk factors could occur in special athlete populations.

Referees demonstrated good aerobic fitness ($\dot{V}$O2max: 44.6 ± 6.1 ml/kg/min range: 25.3–62.4 ml/kg/min) with substantial individual variability. Second division referees were younger, trained more, and achieved longer treadmill exercise time, whereas referees from both divisions had similar $\dot{V}$O2max values. Regarding our physical fitness measurements, large individual differences were observed across many aspects among the referees, despite the fact that they contribute to similar matches.

Three months after a SARS-CoV-2 infection, most athletes achieved satisfactory fitness levels, though exercise-induced abnormalities, including arrhythmias, significant ST-depression, ischemic heart disease, and hypertension were detected in some cases. In athletes with pre-COVID data, self-controlled CPET comparisons were performed, fitness parameters improved, likely due to intensive retraining, though 6 showed decreased capacity. Some cases with SARS-CoV-2-related or non-related pathologies requiring further examinations, treatment, or follow-up were revealed.

In summary, comprehensive cardiac evaluation and systematic screening should be recommended for all athletes at least once during their careers to detect heart conditions and reduce the risk of sudden cardiac death.

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