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THE ROLE OF ELECTROCARDIOGRAPHY AND EXERCISE TESTING IN THE ASSESSMENT OF CARDIOVASCULAR RISK IN ATHLETES AND NON-ATHLETES

Doctoral Dissertation

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Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
ARVC	arrhythmogenic right ventricular cardiomyopathy
AV	atrioventricularis
BMI	body mass index
BP	blood pressure
BPM	beats per minute
CI	confidence interval
CRBBB	complete right bundle branch block
CRF	cardiorespiratory fitness
CV	cardiovascular
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
ECG	electrocardiogram (also electrocardiography, electrocardiographic)
ESC	European Society of Cardiology
FAC	functional aerobic capacity
HCM	hypertrophic cardiomyopathy
HF	high frequency
HR	heart rate
HRV	heart rate variability
IRBBB	incomplete right bundle branch block
LBBB	left bundle branch block
LF	low frequency
LV	left ventricle
LVH	left ventricular hypertrophy

LVEDD	left ventricular end-diastolic diameter
LVEDV	left ventricular end-diastolic volume
MCV	maximal voluntary contraction
nsVT	non-sustained ventricular tachycardia
pNN50	the percentage of differences between successive RR intervals over 24 hours that are greater than 50 milliseconds
QTc	corrected QT interval
RMSSD	the root mean square successive difference
RPE	rating of perceived exertion
RV	right ventricle
RVH	right ventricular hypertrophy
SD	standard deviation
SDNN	the standard deviation of normal to normal ratios
SDNN Index	the standard deviation of all the 5-minute NN interval means
VES	ventricular extrasystole
VLF	very low frequency
WPW	Wolf- Parkinson White syndrome

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1. Introduction

Electrocardiography (ECG) is an essential tool for diagnosis and management of patients with various cardiovascular (CV) diseases. With the development and increased availability of new imaging techniques, however, ECG has lost some of its diagnostic importance. (1) In athletic screening, the usefulness of ECG is also controversial. In athletes, ECG changes are common, and in most cases these reflect benign structural and electrical remodeling of the heart due to physiological adaptation to exercise, a condition which is often referred to as "athlete's heart". (2-4) However, the differential diagnosis between normal physiological changes and pathological abnormalities can be challenging. (5) For regular athletic screening and follow-up, widely available and inexpensive diagnostic methods are needed. In Hungary, ECG is still a cornerstone of routine athletic screening. (6,7) Its significance is based on simplicity, easy availability, short time to perform and interpret, and high informative value in special cases, as well as on the fact that with appropriate evaluation, appearance of pathological ECG signs can forecast the emergence of structural heart diseases years in advance. (8) However, the cornerstone is just part of any foundation, so additional test modalities are often necessary.

With long-term, 24-hour ECG recordings we may not only catch transient arrhythmias and ischemia, but we can also get useful information about autonomic function and predict CV risk. In case of intact autonomic regulation, simultaneous and opposite changes of sympathetic and parasympathetic activity manifest in beat-to-beat fluctuations of heart rate (HR). The extent of these fluctuations shows short-term and long-term changes due to several individual and environmental effects such as physical activity or mental stress and are reduced permanently when autonomic control mechanisms are impaired. Modern Holter monitoring systems are suitable to identify beat-to-beat perturbations of the normal RR intervals, called heart rate variability (HRV) analysis. (9)

Whereas in CV screening of young athletes we are interested primarily in genetic/congenital abnormalities that manifest themselves in the ECG, in adult patients the evaluation is generally performed to discover acquired conditions that have developed over time as a result of poorly managed risk factors and unhealthy lifestyles. While the

ranges of symptoms in young athletes versus adult patients with CV risk factors overlap somewhat, syncope and palpitations are of greater relevance in young athletes, whereas chest pain and dyspnea on exertion are more common and of relatively greater concern in the adult population.

On an exercise test in an adult patient, interpretation of the ST segments provides useful for its diagnostic information, but more important prognostic value can be gained from variables such as functional aerobic capacity (FAC), peak exercise HR and HR recovery. The prognostic predictive value of these parameters has been studied in a wide range of CV populations and has proved to be an independent powerful predictor of mortality. (10-12) Both FAC and HR responses are affected by autonomic function with FAC and peak exercise HR driven by sympathetic tone, while HR recovery is principally related to parasympathetic tone.

Cigarette smoking has profound effects on health. Besides CVD, lung cancer and chronic obstructive pulmonary disease are disabling and life-shortening consequences of cigarette smoking. (13,14) Cigarette smoking reduces FAC and impairs the HR response to exercise. These are important early markers of CV risk. (15,16) Smoking cessation, on the other hand, frequently leads to weight gain and weight-associated comorbidites including hypertension and diabetes. (17) The interplay between smoking status and the predictive exercise factors including FAC and HR recovery are of great potential importance in assessing risk and establishing the benefits of smoking cessation.

The purpose of our studies was to emphasize the importance of ECG in athletic screening, to show the additional diagnostic potential of long-term ECG recording in athletes, to conversely present the predictive value of non-ECG factors – FAC and HR responses – on the exercise test in an adult referral population and to define the role of FAC and HR responses in predicting risk according to smoking status.

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1.1. Cardiovascular Adaptation to Exercise

Physical activity is movement by contraction of specific skeletal muscles of the body, which requires more energy expenditure than resting status. (18,19) This definition includes daily sport activity, physical work, regular training, competitive sports and as well as rehabilitation movement program. All forms of exercise have an effect on the body, specific structural and functional adaptation can be observed according to the type and intensity of sport activity. (2,18) As a result of training, depending on its amount and frequency, acute and chronic sport adaptation can be observed. (2,20) Exercise affects most body systems, including profound effects on the CV system.

As differentiating physiological and pathological sport adaptation is still challenging, we need athletic normal values from studies on large sample size. Because we do not really have such normal values, one possible differential diagnostic method is deconditioning. Cardiac adaptation to exercise may appear after six weeks of intensive training, but as a result of deconditioning these changes disappear. Athletic adaptation is reversible while signs of stuctural heart diseases are irreversible, therefore it may help in the differential diagnosis of borderline cases. (21,22)

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1.1.1. Classification of Sports

Physical activity can be divided into dynamic and static categories according to metabolic characteristics. The dynamic component can be described by predicting maximal oxygen uptake, while the static by maximal contraction volume. According to the ”Morganroth hypothesis”, endurance (dynamic, isotonic, aerobic) sports are for example swimming and long-distance running, while weight-lifting ranks among strength sports (static, izometric, anaerobic). (6,23,24) Dynamic sports cause volume overload, while static ones produce pressure overload on the CV system. The specific cardiac chamber morphology changes are shown in **Figure 1.**

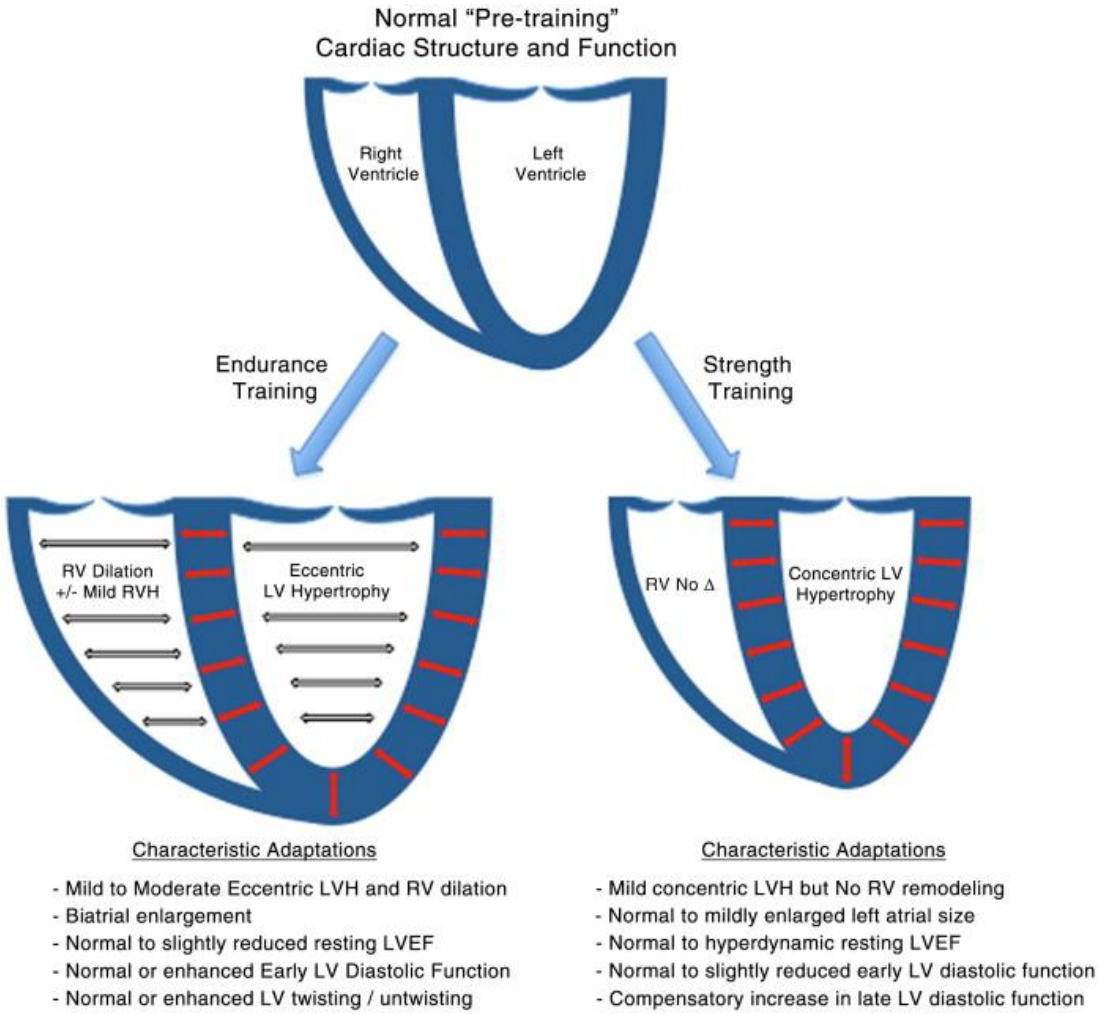

Figure 1. Summary of sport type specific athletic ventricular remodeling. (25)
LV = left ventricular, LVH = left ventricular hypertrophy, RV = right ventricular, RVH = right ventricular hypertrophy, LVEF = left ventricular ejection fraction.

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In compliance with the *36. Bethesda Conference* recommendation, we can classify sports by the proportion of dynamic and static components **Figure 2**. (2,18,26-28)

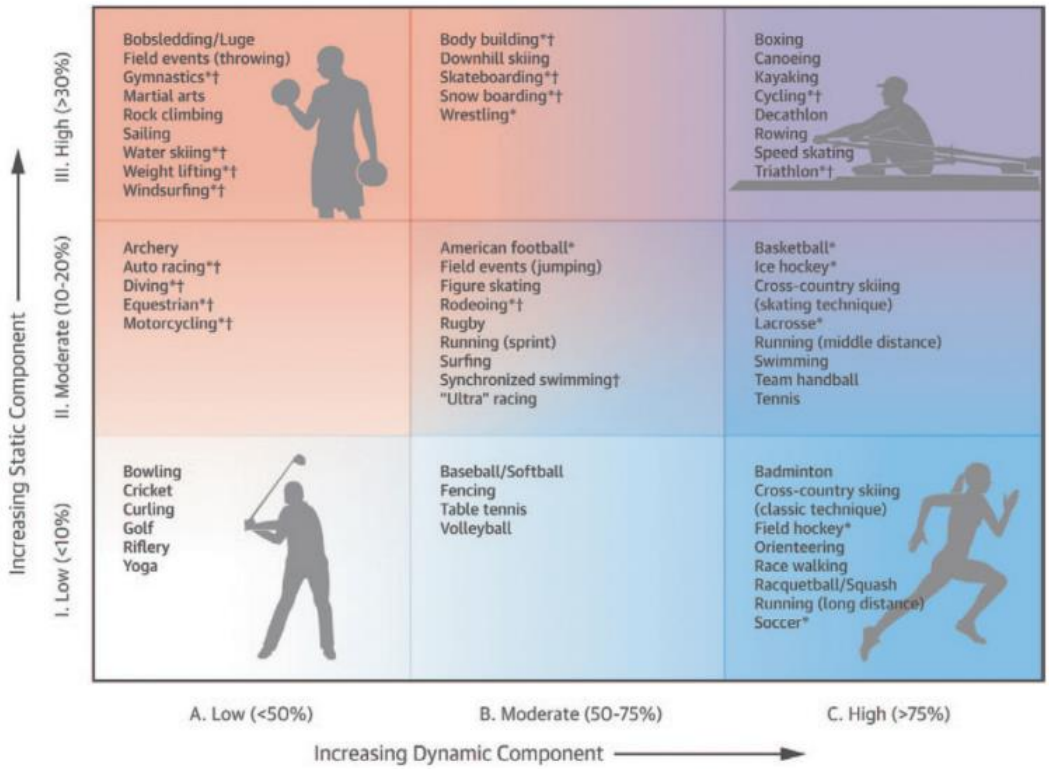

Figure 2. Classification of sports based on peak static and dynamic components achieved during competition. The increasing dynamic component is defined in terms of the estimated percentage of maximal oxygen uptake (VO_2max) achieved and results in an increasing cardiac output. The increasing static component is related to the estimated percentage of maximal voluntary contraction reached and results in an increasing blood pressure load. The lowest total cardiovascular demands (cardiac output and blood pressure) are shown in the palest color, with increasing dynamic load depicted by increasing blue intensity and increasing static load by increasing red intensity. Note the graded transition between categories, which should be individualized on the basis of player position and style of play. *Danger of bodily collision. †Increased risk if syncope occurs. (27,28)

Cycling or rowing are good examples of combining static and dynamic activity, but in most sports endurance and isometric elements are both represented in the training program. (18) Moreover, different position players may have quite different CV loads. Nevertheless, there are some weaknesses of this classification, namely that there is no guideline about psychic stress during competition and about different environmental circumstances. (28)

1.1.2. Acute Adaptation to Exercise

To provide enhanced energy of muscle contraction during physical activity, breathing intensity increases with more oxygen uptake in the lungs. As pulmonary blood flow increases with enhanced breathing, other parts of the vascular system show adaptation to exercise. (20,29,30) Acute CV adaptation includes chronotrop mechanisms – increased HR – and inotrop mechanisms – enhanced contractility power. (29,31) HR increase during exercise is regulated by the autonomic nervous system characterized by rapid and sustained parasympathetic withdrawal coupled with sympathetic activation. Peak HR is affected by several factors like age and sex and may actually slightly decrease with aerobic training. Stroke volume increases significantly both at rest and during exercise with prolonged aerobic training. Cardiac output – the product of stroke volume and HR – may increase 5- to 6-fold during a maximal exercise effort. Increased cardiac output and redistribution of circulating blood provides increased perfusion of muscles and heart with stable cerebral blood flow (**Figure 3**). (29,31) Blood flow in the gut and skin decrease during heavy exercise, though skin blood flow will increase during prolonged exercise in hot environments, while blood flow in other organ systems remains relatively constant.

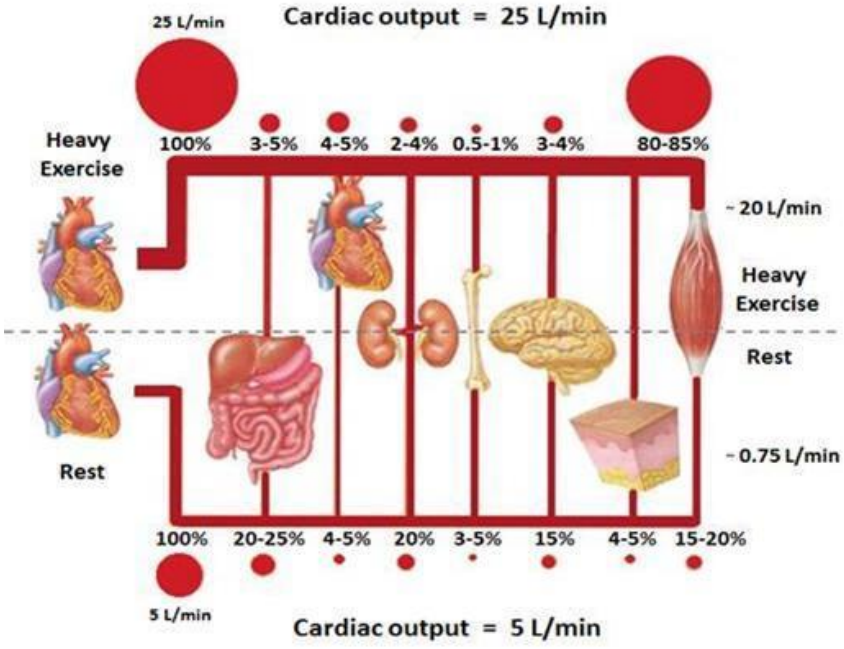

Figure 3. Distribution of cardiac output at rest and during heavy exercise. (32)

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1.1.3. Chronic Adaptation to Exercise

As a result of long, repeated bouts of physical exercise, structural and functional adaptation can be observed in the CV system. This includes prominent cardiac remodeling called athlete's heart (**Figure 4**). (2,30,33) The type and magnitude of changes depends on the type and amount of exercise and also on sex and genetic factors.

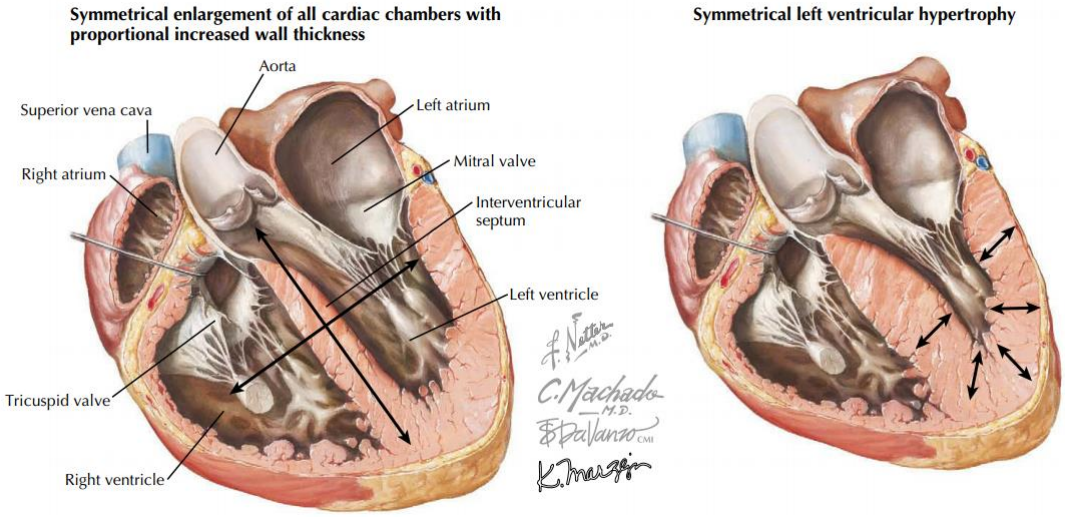

Figure 4. Morphology of left ventricular hypertrophy in athletes. (33)

Cardiac hypertrophy is the most pronounced feature of athlete's heart, which affects the entire heart but mostly left ventricular (LV) wall thickening can be observed. Besides muscle mass increase, capillary density increases too. (2,29,33,34) While wall thickening as a consequence of static exercise is due to pressure overload, dynamic exercise results in volume overload, which manifests itself in increased diameters. Henschen's definition of athlete's heart: "an enlargement of the heart which can perform more work than a normal heart." (2,35) It is very important to distinguish the physiological left ventricular hypertrophy (LVH) of athlete's heart from the pathological LVH of hypertrophic cardiomyopathy (HCM); this can be accomplished with appropriate diagnostic methods. (34,36) The difference between physiological athlete's heart and pathological LVH is the structure and amount of pathological cells and tissue, whose consequences worsen first the diastolic and then the systolic function in pathological LVH. (30)

In recent years, cardiac remodeling has been studied with several imaging techniques. Echocardography studies showed that ventricular diameters are related to sports type and intensity. (4,37) The most pronounced increases can be observed in rowing, cross country

skiing, cycling and swimming. However, adaptative changes may be different, as almost all athletes have some evidence of athlete's heart including LV dilatation and increased wall thickness. (21) Marked (> 60 mm) LV end-diastolic diameter dilatation may be present in only 15% of athletes, while > 13 mm wall thickness is only present in 2% of the athletes (**Figure 5/A and 5/B**). These two parameters are generally lower in women compared to men. (2,34)

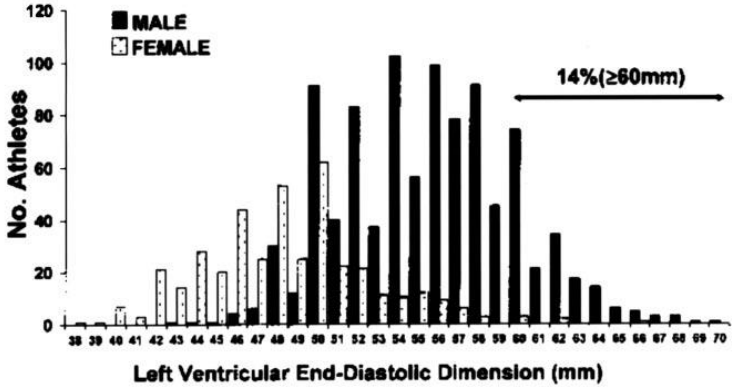

Figure 5/A. Left ventricular end-diastolic dimensions in male and female athletes by echocardiography. (2)

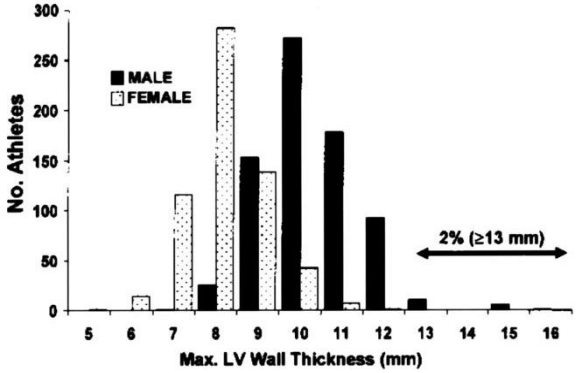

Figure 5/B. Left ventricular wall thickness in male and female athletes by echocardiography. (2)

Increased LV diameter can be observed after one week of endurance training, while the increase of myocardial mass is slower, correlating with training years and maximal oxygen uptake. Enhanced blood volume increases volume overload of the heart and

contributes to the rapid increase of heart dimensions. Athletes have higher LV end-diastolic volume with increased cardiac stroke volume, so they can provide the resting cardiac output with lower HRs. (2,3,30)

It is important to mention here that these structural adaptations to chronic exercise also affect the resting ECG, making it potentially more challenging to distinguish healthy athletes from those with cardiac diseases.

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1.1.4. Autonomic Adaptation to Exercise

Cardiovascular autonomic function also shows acute and chronic adaptation to physical exercise through the regulation of HR, blood pressure (BP) and circulatory redistribution mediated by sympathetic and parasympathetic nervous systems.

At the beginning exercise, HR increases rapidly, mainly due to the withdrawal of vagal activity. As the workload increases, HR increases due to further vagal withdrawal and concomitant sympathetic activation. (38-41)

The complexity of exercise induced long-term CV adaptation is well reflected by lower HR at rest and during submaximal exercise with unchanged or even slightly lower peak HR remains. (2,3,18) As a consequence of structural adaptation, in athletes a given increase in cardiac output requires less increase in HR due to the maintenance of a larger stroke volume. On the other hand, HR may be reduced during submaximal exercise due to a lower intrinsic HR, as a result of sympathetic activity decrease with less circulating catecholamines and a greater parasympathetic influence. (42) At the same time, regular physical activity also reduces the sympathetic effect on the sinoatrial node. (39,40) Besides lower HRs, chronic autonomic adaptation may also manifest in conduction abnormalities such as transient second degree AV block and increased ventricular ectopy that might mimic underlying cardiac disease.

Underdeveloped cardiac autonomic adaptation may be a warning sign of underlying cardiac abnormality as sympathovagal imbalance and impaired baroreceptor function may preceed ventricular arrhythmias and myocardial ischemia and have been associated with an increased risk of mortality. (43-45)

1.2. Sudden Cardiac Death in Athletes

In recent years, sudden cardiac death (SCD) has become a center of focus in the media, as several prominent US collegiate and professional athletes literally "died on the screen". Although, the number of athletic SCDs is relatively small, these deaths represent an important and emotionally charged public health issue.

The incidence of SCD is greater in athletes compared to non-athletes who perform recreational sports. (46-50) Competitive sports activity enhances the risk of SCD by 2.5-fold in adolescents and young adults. (47,51-53) The difference in incidence may be explained by the fact that the intensity and duration of physical activity is likely much higher in competitive versus recreational sports, but use of performance-enhancing substances may also play a role in some of the deaths. We also cannot rule out an ascertainment bias in that competitive sports are more closely scrutinized and deaths witnessed and well-documented, whereas deaths in recreational activity may more likely be undocumented and unreported. According to a prospective population-based study from Italy, the incidence of sudden death is 2.3 (2.62 in males and 1.07 in females) per 100 000 athletes per year from all causes, and 2.1 per 100,000 athletes per year from CVDs. (51) In the United States the prevalence of SCD is in the range of 1:100,000 to 1:300,000 high school–age athletes, while among older athletes the frequency of SCD due principally to coronary artery disease (CAD) may exceed that of younger athletes (1:15,000 joggers and 1:50,000 marathon runners). (52,54-56) The difference in incidences between Italy and the United States includes that studies from the United States probably underestimated the prevalence of sports-related SCD because they relied on reports from individual schools and institutions, or on media accounts. Another reason could be the different underlying pathological substrates which might reflect differences also in ethnic and genetic factors (specifically arrhythmogenic right ventricular cardiomyopathy - ARVC) along with higher mean age and higher level of participation of Italian competitive athletes compared with U.S. high school and college participants. (52,57,58)

SCD in athletes shows a clear gender difference with male predominance up to 10:1. (50,52,59,60) This may be explained by the higher participation rate of male compared to female athletes in competitive sports, by the higher intensity with more intense pressure

of training load and level of athletic achievement of males, longer competitive seasons, as well as the lower prevalence of cardiac abnormalities capable of causing SCD in females. (61) Greater use of performance-enhancing drugs and supplements among male athletes may also play a role. More recently, male gender was reported to be, in itself, a risk factor for sports-related SCD. (48,49,52,57,58)

In Hungary, there are no published statistical data about the incidence of SCD during sports, but the estimated frequency of sports-related death is not likely higher than the Italian experience. (18,62)

SCD occurs more frequently in certain sports. In the United States, basketball – primarily men's basketball (63) – has the greatest incidence, whereas in Europe soccer predominates. (52)

SCD is usually the result of an interaction between an acute trigger and underlying heart disease (substrate). (64,65) Emotional stress, environmental factors, myocardial ischemia, sympathetic-vagal imbalance, and hemodynamic changes may be acute triggers for life-threatening ventricular tachyarrhythmias and SCD during sports. (66) In young athletes (<35 years of age), the most common cause of SCD is underlying congenital cardiac disease, such as cardiomyopathies and congenital coronary anomalies (**Figure 6**). (67)

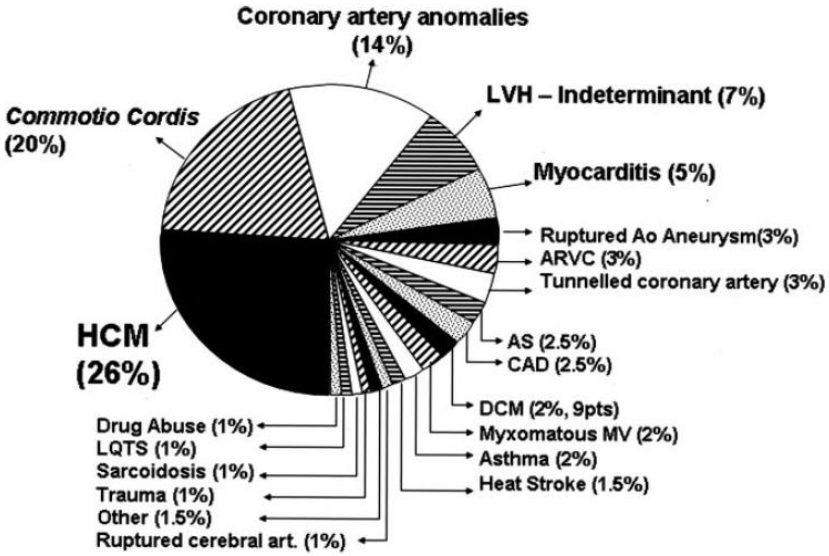

Figure 6. Causes of sudden cardiac death in young athletes. (2,67)
HCM = hypertrophic cardiomyopathy, LVH = left ventricular hypertrophy, ARVC = arrhythmogenic right ventricular cardiomyopathy, AS = aortic stenosis, CAD = coronary artery disease, DCM = dilated cardiomyopathy, LQTS = long QT syndrome.

In the presence of heart disease, intensive and systematic athletic training itself may promote progression or worsening of the arrhythmogenic substrate (either structurally or electrically) therefore increasing the risk of SCD. (66) For example, in patients with HCM, recurrent episodes of exercise-induced myocardial ischemia during intensive training may result cell death and myocardial replacement fibrosis, which in turn enhances ventricular electrical instability. (68) In patients with ARVC, regular and intense physical activity may provoke RV volume overload and cavity enlargement, which in turn may accelerate fibrofatty atrophy. (69)

Geographical differences have been reported in the causes of SCD between Europe and the US in young athletes. In the US the most common cause is HCM, while in Europe ARVC. These differences are more likely to be related to the differences in pre-participation screening methods in the identification of athletes at a higher risk, rather than reflecting a truly different etiology. In the US, African-American males have higher rates of SCD during sports than white males.

Other common causes are genetic diseases as ion channelopathies (long QT syndrome, Brugada syndrome, short QT syndrome and cathecholaminerg polymorphic ventricular tachycardia). These deaths occur most commonly in team sports such as basketball and football, which have the highest levels of participation. (52) Blunt chest trauma also may cause ventricular fibrillation in a structurally normal heart; this is known as commotio cordis. (70,71)

In older athletes (35 years and older), atherosclerotic CAD is the most common cause (85%) of SCD.(56) They are individual athletes – such as long distance runners – rather than members of organized team sports. (52) Besides known risk factors of ischemic heart disease, in athletes myocardial ischemia may be induced by increased wall stress from increased HR and BP, exercise induced coronary artery spasm, decreased coronary perfusion as a result of shortened diastolic filling time and increased myocardial oxygen demand. These mechanisms may induce acute coronary artery plaque disruption, including plaque rupture or erosion, with acute thrombotic occlusion. (72) An increase in thrombogenicity also could contribute to coronary thrombosis after plaque rupture or erosion. (73) Myocardial ischemia causes electrically inhomogeneous areas, scars which can be disposed to develop malignant ventricular arrhythmias and fibrillation. All of the

above-mentioned abnormalities may induce malignant ventricular arrhythmias, mainly (65-80%) ventricular fibrillation, which is the definite cause of SCD.

Diagnosing underlying cardiac diseases could potentially prevent some cases of SCD during sports. Athletes could be treated for example with surgery for anomalous coronary arteries in younger athletes or percutaneous coronary intervention or bypass surgery in older athletes. Other athletes with less treatable conditions like HCM could be disqualified or rechanneled into less strenuous sports. Recently published guidelines from ACC/AHA also allow continued participation for some athletes with arrhythmogenic substrate after the institution of appropriate therapies including implantable cardiac defibrillators.(74,75) Therefore, all athletes should undergo some sort of pre-participation CV screening. However, the elements of the screening have not been standardized across countries. Moreover, evaluation of athletes raises diagnostic difficulties, particularly differentiating between physiological adaptation to exercise and pathological conditions, so some normal athletes may inadvertently be disqualified while some abnormalities might be classified as "normal variant". Economics of screening is a major issue, considering the high cost of some cardiac tests versus the very low rates of SCD (1-2 per 100,000 athletes per year) during sport. In US, screening is conducted according to an algorithm whereby history and physical exam determine who gets an ECG or further cardiac tests, whereas general screening with ECG ± echocardiography may be employed in Europe or in some American professional sports (Women's NBA, for example).(76) Other questions to be addressed include frequency of screening and at what age screening begins. Is one evaluation to look for cardiac abnormalities when the athlete first begins high level training and competition sufficient, or does evaluation need to be repeated annually? There may also be medical-legal issues in the case of athletes who experience SCD after being screened or with athletes who are disqualified from sports but independently produce contrary evidence that they do not have cardiac abnormalities.

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1.3. ECG Screening in Athletes

The role of pre-participation screening is to identify or raise the suspicion of those underlying CVDs, abnormalities and CV risk factors which are responsible for athletic field deaths so as to disqualify – or in some cases provide ameliorative treatment to – athletes at risk. We expect that applying this strategy may prevent some cases of SCD. (77-80) In Hungary, similarly to other developed European countries, pre-participation screening is mandatory once a year for athletes over 18 years of age and every six months under 18 years of age. (7,81) The basic examinations include family and personal history, physical examination with BP measurement, and resting 12-lead ECG. Personal history is performed on a detailed questionnaire which contains several questions about the health status of the athlete, such as symptoms during exercise, CV risk factors, and medications. In addition to personal history, there is a separate section for family history designed to identify possible inherited CVDs and assess the presence of SCD in the family. (7,81) In Hungary, resting 12-lead ECG is an essential part of pre-participation screening. Nevertheless, imaging diagnostic techniques such as echocardiography or cardiac MR, are also performed in case of symptoms or positive findings on basic exams as shown on **Figure 7**. Athletes diagnosed with clinically relevant CV abnormalities are managed according to available guidelines for assessing athletic risk.

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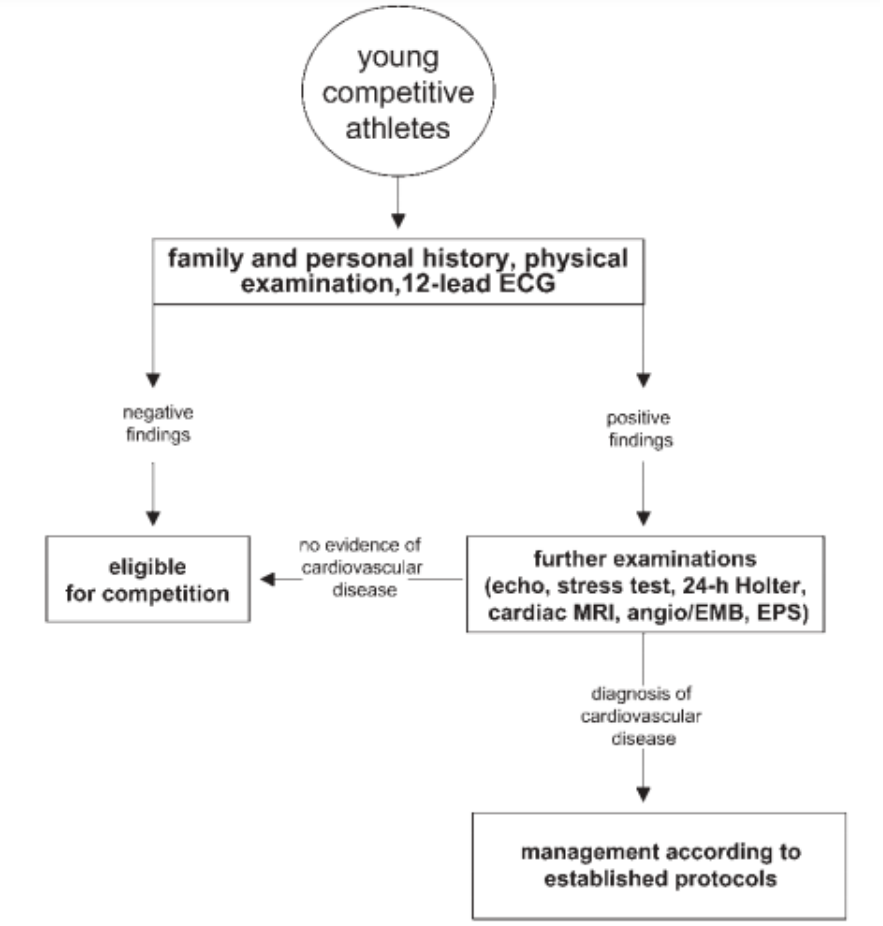

Figure 7. Flow diagram illustrating pre-participation screening protocol for young competitive athletes. (80)
EMB = endomyocardial biopsy, EPS = electrophysiological study, MRI = magnetic resonance imaging.

1.3.1. Resting 12-lead ECG

ECG changes in athletes are common and in most cases reflect benign structural and electrical remodeling of the heart due to physiological adaptation to physical training, as a part of "athlete's heart". (2,3,5,82) The majority of disorders associated with an increased risk of SCD can be suggested or identified by resting ECG abnormalities. Moreover, ECG changes may preceed years in advance of the abnormalities caused by structural heart disease.(8) Resting ECG is an essential part of pre-participation screening in Hungary, but the US and Europe have treated the need for universal ECG differently. In Europe, long-term Italian (specifically, Veneto region) experience has demonstrated that pre-participation screening with medical history and physical examination has limited sensitivity to detect athletes at high risk, but the implementation of ECG to the screening protocol increases its sensitivity and is an effective way of identifying athletes with potentially lethal CVDs and ultimately saves lives. (83-87) This screening algorithm, which has been used for pre-participation screening in Italy for over a 25-year period, has proved adequate sensitivity and specificity for detecting athletes affected by potentially dangerous cardiomyopathy or arrhythmia, and has led to a decreased mortality of young competitive athletes by ~90%, mostly by preventing SCD from ARVC which is common in this region but has a low prevalence elsewhere. **Figure 8**. (80,88-90)

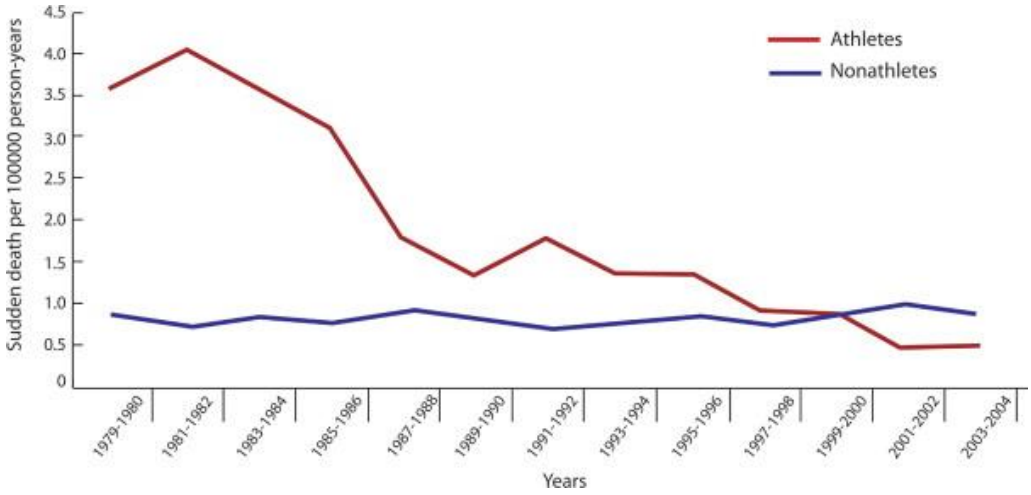

Figure 8. Annual incidence rates of sudden cardiac death in screened competitive athletes and unscreened nonathletes aged 12 to 35 years in the Veneto Region of Italy (1979-2004). (89)

However, in the US concerns have been raised and the usefulness of ECG was questionable because of cost-effectiveness and low specificity with high level of false positive results. (78,91-93) Americans may be more sensitive to the issue of inappropriate disqualifications and generation of expense downstream evaluations and the anxiety they produce in otherwise healthy athletes with isolated ECG abnormalities. In recent years some American groups have accepted the use of universal ECG screening and have stated that ECG added to focused CV history and physical examination may be cost-effective and improve the overall sensitivity of pre-participation screening. (94,95)

Digital ECG recording has been spreaded recently, therefore serial comparison of previous ECG recordings may help to identify and highlight changes in order to make clinical decisions and it may decrease the high false positive results.

The original recommendations for ECG interpretation in athletes were published in 2010 by the European Society of Cardiology (ESC). (96) Athletic ECG changes are common and usually reflect structural and electrical remodeling of the heart. (97) However, ECG abnormalities may be an expression of an underlying heart disease. (98) It is important to correctly distinguish between physiological ECG changes and potentially pathological ECG abnormalities. Over the last decade, ECG interpretation standards have evolved quickly. (99) In 2013, an international group of sports cardiology experts updated contemporary standards for ECG interpretation in athletes, called ”Seattle Criteria”. (100) The ”Seattle Criteria” significantly improved the specificity of ECG screening for detecting CVD associated with SCD, by accounting for specific benign repolarization anomalies associated with black ethnicity and designating less conservative limits for an abnormal QT interval. (101,102) In 2014, the ”Refined Criteria” have been associated with further reduction in false positives - isolated atrial enlargement, axis deviation and right ventricular hypertrophy (RVH) - without compromising sensitivity. (101) While comparing the three guidelines, the application of ”Refined Criteria” results in a significant increase in specificity when compared to the “ESC” and the “Seattle Criteria”, while retaining the same sensitivity. This reduces the amount of abnormal ECGs from 12.7% - 22.3% with the ESC criteria to 1.9% - 6.6% with the “Refined Criteria”. Moreover, new ECG interpretation guidelines are associated with a cost reduction of up to 21% without compromising sensitivity to detect serious cardiac disease. (103)

In 2017, an international consensus statement was published about ECG interpretation in athletes, which provides expert opinion-based recommendations of specific ECG abnormalities and secondary evaluation for conditions associated with SCD. (104)

Figure 9 lists the international standards for ECG interpretation. (104) The consensus document distinguishes normal, abnormal and borderline ECG findings. Athletes having two or more borderline ECG findings require further evaluation.

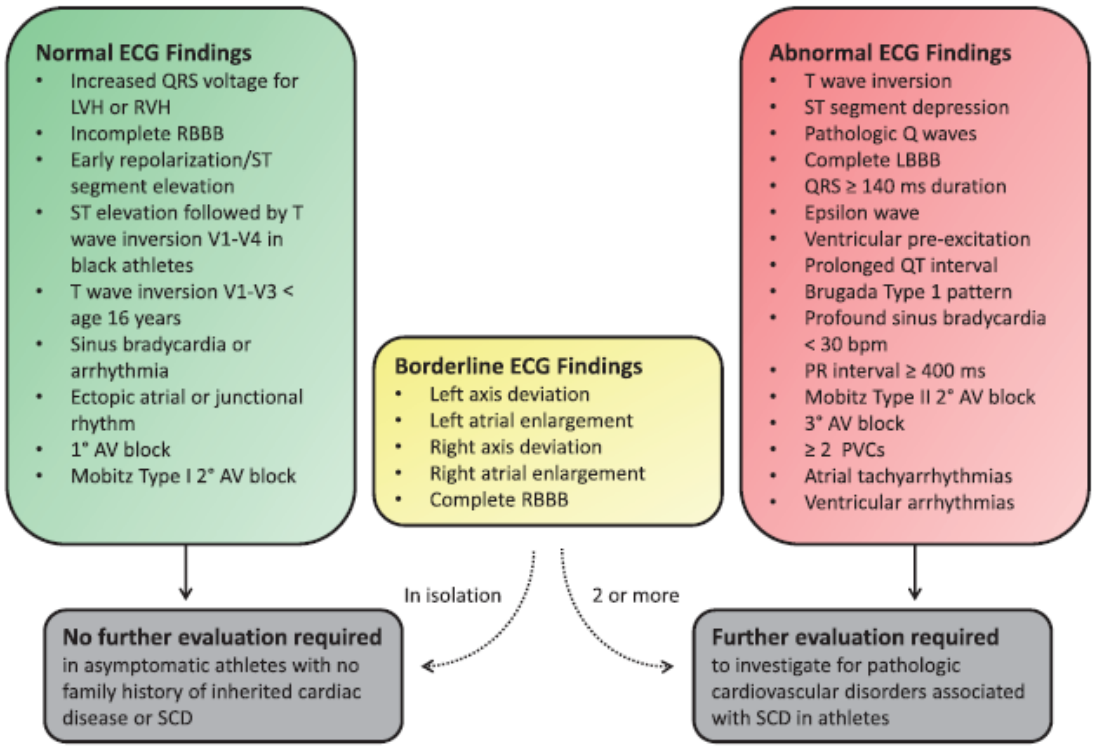

Figure 9. International consensus standards for electrocardiographic (ECG) interpretation in athletes. (104)
AV = atrioventricular, LBBB = left bundle branch block, LVH = left ventricular hypertrophy, RBBB = right bundle branch block, RVH = right ventricular hypertrophy; PVC = premature ventricular contraction, SCD = sudden cardiac death.

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On a characteristic athletic ECG (**Figure 10**) resting sinus bradycardia, first degree AV block and early repolarization are common ECG signs resulted by autonomic adaptation of the heart (increased vagal tone and decreased sympathetic activity). Besides these evidences of electrical sport adaptation, structural adaptation can also be observed as signs of LVH. These physiological changes have to be differentiated from pathological abnormalities such as pathological T-wave inversion, q waves, conduction abnormalities and arrhythmias, which may be a sign of structural heart disease. (105-108)

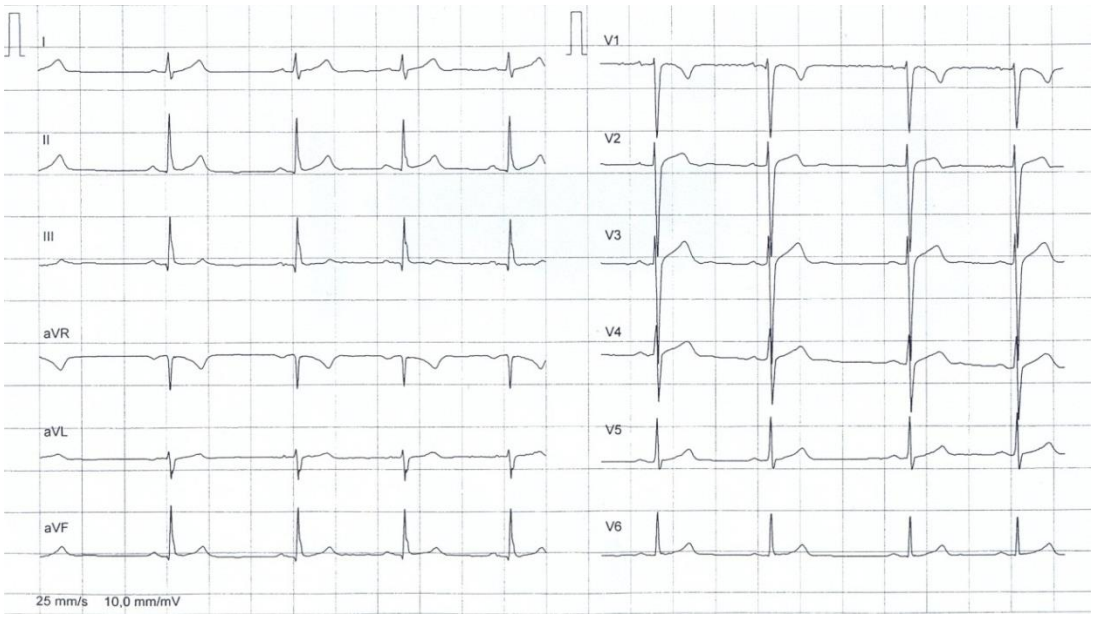

Figure 10. Resting ECG recording of a Hungarian Olympic champion. Sinus bradycardia, heart rate: 51/min, marked sinus arrhythmia, central axis, left ventricular hypertrophy (Cornell criteria), V2-V3: 1 mm J-point elevation.

1.3.2. Holter ECG

Besides evaluation of morphologic ECG changes on the resting ECG, periodic alterations of ECG rate, rhythm, and morphology could provide information about underlying conduction diseases and transient ischemic changes of the heart. For this we need long-term ECG recording and detailed analyses of indirect signs such as HRV. Another advantage of Holter ECG is that we can monitor ECG features during different parts and activities of day and night. Most widespread functions of Holter ECG are evaluation of HR profile during resting and training, detecting brady-and tachyarrhythmias and recognizing transient ST-T changes. Arrhythmias can be described thoroughly with onset, lengths, frequency, relation to exercise and symptoms. Besides these basic, widely known functions, modern Holter systems have special functions such as QT analysis, T-wave alternant analysis and evaluation of autonomic function with HRV.

We have some earlier unpublished data about Holter ECG changes in athletes. On a Holter screening of healthy, asymptomatic athletes, we revealed ECG changes in more than 60% of the cases, which could not be detected by a standard resting ECG. Certainly, Holter changes we detected were mostly non pathological. Intermittent first degree AV-block, transient junctional rhythm and Wenckebach phenomenon with non-significant pausa are common signs of a consequence of increased vagal tone. However, Holter screening revealed pathological, sport-unrelated changes too, such as atrial and ventricular arrhythmias, transient high degree AV block and intermittent repolarization changes. Athletes with these abnormalities underwent a detailed cardiac examination, but no structural heart disease was verified. We recommended regular follow-up with Holter ECG control. In two asymptomatic athletes, Holter ECG identified accessory pathway conduction. Electrophysiology exam and catheter ablation was performed.

Heart Rate Variability (HRV) Analysis

With the availability of new, digital modern 24-hour, multichannel ECG recorders, HRV has the potential to provide additional valuable insight into physiological and pathological conditions and to enhance risk stratification. (9) SCD may be triggered by changes of autonomic regulation. In case of intact autonomic nervous function, simultaneous and opposite changes of sympathetic and parasympathetic activity manifest in oscillation in the interval between consecutive heartbeats. The extent of these fluctuations shows short-term and long-term changes due to several individual and environmental effects such as physical activity or mental stress and is reduced permanently when autonomic control mechanisms are impaired. Modern Holter monitoring systems are suitable for detecting beat-to-beat fluctuations of RR intervals (**Figure 11**), called HRV analysis. (9)

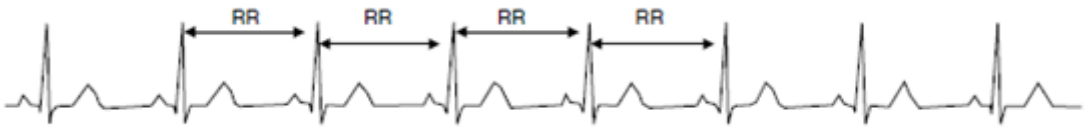

Figure 11. Beat-to-beat perturbations of RR intervals. (9)

The physiological background of HRV can be defined as the autonomic nervous system with sympathetic and parasympathetic regulation maintaining CV homeostasis by responding to beat-to-beat perturbations sensed by baroreceptors and chemoreceptors. (109) Arterial and venous BP are altered continuously as a result of the cyclic variation in intrathoracic pressure associated with respiratory movements, and also because of the fluctuations in peripheral vascular resistance resulting from regional blood flow autoregulation. (110)

The variations in HR may be evaluated with several methods. The RR variations can be evaluated by time domain and frequency domain methods. In a continuous ECG recording, each QRS complex is detected, normal-to-normal (NN) intervals (that is, all intervals between adjacent QRS complexes resulting from sinus node depolarizations) are determined. Simple time domain variables that can be calculated for example, the mean NN interval, the mean HR, the difference between the longest and shortest NN interval. Short time HRV parameters (RMSSD and pNN50) reflect parasympathetic activity, while SDNN and SDNN Index show all frequency changes of the examined time **Table 1.** (9,110)

Table 1. Time domain parameters of heart rate variability and their definitions. (9)

Time- domain parameter	Definition
SDNN (ms)	the standard deviation of normal to normal ratios
SDNN Index (ms)	the standard deviation of all the 5-minute NN interval means
RMSSD (ms)	the root mean square successive difference
pNN50 (%)	the percentage of differences between successive RR intervals over 24 hours that are greater than 50 ms

While analyzing the HRV frequency domain, the spectral analysis of HR signals displays their power spectrum density and marks in a plot the relative contribution (amplitude) of each frequency, each plot including a minimum of three peaks. The fast periodicities in the range 0.15-0.4 Hz (HF) are the result of the influence of the respiratory phase on the vagal tone. The low frequency periodicities (LF) situated in the range of 0.04-0.15 Hz, are produced by baroreflex feedback loops, affected by both sympathetic and parasympathetic modulation of the heart, and very low frequency periodicities. Accordingly, in the frequency range less than 0.04 Hz, the periodicities have been variously ascribed to modulation by chemoreception, thermoregulation and the influence of vasomotor activity. The total spectrum (TP 0.01-1.0 Hz) reflects the total variability, which includes VLF besides LF and HF. The area that can be found under the power spectral curve in a particular frequency band is considered to be a measure of HRV at that frequency. According to the Task Force report, the ECG signals analyzed have to meet several technical requirements in order to obtain reliable information. For grounded results, the ectopic beats, arrhythmic events, missing data and noise effects should be properly filtered and omitted. While carrying out short-term investigations, frequency domain methods must be preferred, additionally frequency and time domain methods are well correlated to each other. SDNN correspond to TP, SDNN Index is correlated well with VLF and LF while pNN50 and RMSSD is proportional to HF. (111)

Intensive research of HRV - as a marker of cardiac autonomic function - has been carried out in the past few decades. (40,41,53) HRV has been utilized to characterize adverse CV adaptation in certain disease entities such as ischemic heart disease and heart failure. (112,113) The alteration of autonomic influences cannot just present a marker for psychophysiological state but can also be a trigger mechanism of life-threatening

arrhythmias in specific situations. (114,115) The clinical importance of HRV became accepted in the late 1980s, after it was confirmed that HRV is a strong and independent predictor of mortality after an acute myocardial infarction. (116-118) Presumably in connection with its arrhythmogenic effects, decreased HRV has been shown to be a strong and independent predictor of mortality in other CVDs as well. (119)

Several trials examined the influences of physical activity on HRV. The enhancing effect of training on HRV was observed in healthy participants as well as in CAD, heart failure, obesity, type-2 diabetes mellitus and following myocardial infarction. (120,121) In healthy participants, baseline autonomic status has been shown to be an important determinant of cardiac autonomic response to exercise. (122)

HRV analysis has also been used for the testing and follow-up of athletes. It is well known that long-term training increases HRV. (123) Training for sports competition promotes a long-term increase in parasympathetic tone with concomitant inhibition of sympathetic tone in the resting state. (124) Athletes generally manifest resting bradycardia - often with first or transient second degree AV blocks and nodal rhythms. (125) With exercise, however, HR increases appropriately, and the conduction abnormalities disappear. As a characteristic of athletic training, HRV analysis may be useful for following CV fitness development and determining optimal training intensity. (126-128) Short-term HR monitoring and calculation of frequency-domain parameters of HRV has been suggested to be a useful method for training load quantification (129), the testing of psychophysiological adaptation to different phases of training (130) and recovery monitoring of injured athletes. (131) On the other hand, the decrease of HRV is used as a marker of overtraining and exhaustion. (114,119) Following high eccentric strength training, the decrease of specific high frequency domain HRV parameters beside the increase of low frequency HRV values was supposed to indicate autonomic imbalance towards sympathetic modulation predominance in healthy older men. (132) Moreover, those athletes who were trained taking into account the changes of their HRV parameters showed better athletic achievements compared to the ones with fixed training plans that did not include adjustment for HRV. (115)

However, the methodology of measuring and calculating HRV has not been standardized due to differing recording time and the variability of measured parameters. Short-term

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HRV measurements of 1 to 10 minutes can be affected by several transitional effects even in maximally controlled testing conditions. For this, long-term HRV analysis during all-day activity of up to 24 hours using Holter monitoring could be a more stable and reproduceable measure of the actual autonomic state of athletes, besides several other advantages of Holter ECG screening. Moreover, while short-term HRV measurements are often limited to frequency-domain analysis, long-term HRV measurements offer the opportunity of accurate evaluation of time-domain HRV parameters as well. However, there are at present very limited data on long-term HRV measures and time-domain HRV parameters of athletes, although time domain measures are considered to be more consistent than frequency domain parameters to describe chronic autonomic adaptations in athletes. (133)

1.3.3. Exercise Testing

Exercise testing is one of the most common non-invasive techniques to diagnose CAD, determine its prognosis and follow patients longitudinally. Applying exercise testing, we can assess FAC, exercise related symptoms and hemodynamic changes (HR and BP). In athletes, we can detect ECG abnormalities not present at rest, including exercise induced arrhythmias, conduction disorders and myocardial ischemia. We can also identify masked hypertension. Nevertheless, exercise testing is not the part of routine pre-participation screening of athletes. It requires special facilities, adds expense to the screening, and brings up interpretative conundrums similar to the resting ECG and various cardiac imaging tests. In non-athletes, particularly older individuals with CAD risk factors and, especially, symptoms that suggest CAD, exercise testing is widely employed.
Exercise HR responses have been studied for many years, without full agreement about differences in HR by age in men versus women. Peak exercise HR has been estimated as 220 minus age for both men and women since an initial report in the 1970s by Fox et al,(134-138) though more recent studies question the accuracy of this formula, particularly in women. (139) The number of women undergoing exercise testing has increased in recent years, so laboratories have more experience testing women. Also, sports activities for women have increased, so women are more accustomed to high levels of exertion. Although these important facts are known, women have been underrepresented in most CV studies, including those involving exercise testing.

HR responses to exercise have been studied in different patient populations and have proved to identify higher risk patients. (11,12,116,128,135,140-142) Smoking is one of the major risk factors for CV disease (CVD) and all-cause mortality. As the leading preventable cause of death, smoking accounts for more than 480,000 deaths every year in the United States.(143) Therefore, smoking cessation is one of the most important steps in CVD prevention. However, quitting smoking may cause weight gain and increase the risk of weight-associated comorbidities such as diabetes and hypertension, thus potentially attenuating the benefits of quitting. (144-146) Moreover, obesity itself is also a strong risk factor for incident CVD. Exercise is another most important tool of both primary and secondary prevention. It can help in weight loss and has several well-known protective effects. Lee et al. proposed that exercise may have a protective effect in men

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regarding cancer mortality by smoking status, after his study there was only one large study which investigated the associations between exercise and smoking habits. (147) The researchers found that exercise reduces mortality by around 30% in smokers and past smokers. (148)

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1.4. Semmelweis Bridge Project

Semmelweis Bridge Project (TÁMOP 4.2.2-08/1/KMR) was established to perform translational research in the area of CVDs through international scientific cooperations. It provides possibilities to athletic screening with the highest technological equipment to assess CV risk. At Semmelweis University Heart and Vascular Center we aimed to perform detailed basic and clinical research of athletic adaptation with differentiating physiological changes and pathological abnormalities. In the frame of this extended CV screening, all athletes underwent personal and family history screening, physical examination, ECG, laboratory testing, 24-hour Holter monitoring, echocardiography and cardiac MR.

In order to investigate CV risk in athletes, non-athletes and patients, we initiated a cooperation with the Mayo Clinic Cardiovascular Health Clinic, which has the largest exercise test laboratory in the world. The Mayo Integrated Stress Center Database (MISC) contains exercise testing data about almost 140.000 patients with more than 200.000 exercise tests covering approximately 32 years, which has thus provided a solid resource basis of the different composite populations for our own research.

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2. Objectives of our Studies

1. Our first aim was to study electrocardiographic adaptation to sports-specific training.
    - We conducted a detailed prospective observational study of athletes in which we performed ECG analysis
    - We documented the prevalence of physiological, common ECG changes, potentially pathological, training-unrelated ECG changes and pathological abnormalities in a composite sample of healthy, asymptomatic Hungarian athletes. (149)
2. Our hypothesis was that training adaptation of the ECG depends upon autonomic nervous system adaptation, which can be determined by analysis of HRV.
    - Consequently, we measured HRV in our prospective cohort of young asymptomatic elite and masters athletes and young non-athletic controls during long-term Holter ECG monitoring.
    - Our second aim was therefore to investigate training-related, sport-specific differences in HRV.
    - Moreover, we targeted to determine normal distribution curves and lower cut-off values for the studied HRV parameters to provide the lower limit of normal athletic values in the elite athletes. (150)
3. Subsequently, we also analyzed a large cohort of adult, non-athletic patients without CVD, who underwent clinical exercise testing.
    - Our aim was to determine factors including age, sex, cardiorespiratory fitness (CRF) and comorbidities that affect exercise HR.
    - After the exclusion of HR modifying factors we aimed to determine exercise HR responses in men and women according to age (151)
4. Finally, using our large exercise testing database with a fully ascertained total, CV, and cancer mortality during long-term follow-up
    - We proposed to study the effect of smoking on weight-associated comorbidities and mortality in patients without baseline CVDs.
    - We equally sought to determine whether better CRF on a stress test reduces mortality risk in past and current smokers.

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3. Methods

3.1. Participants

3.1.1. Study Population of Athletic ECG Projects

Healthy asymptomatic elite, non-elite and master athletes and controls were studied. Our athlete group was stratified according to training intensity and frequency. Athletes were categorized into two groups according to their level of activity assessed in a detailed questionnaire (registering the year they started the competitive sport activity, the number of training sessions per day and per week, lengths and types of training, phase of training and best results). The studied elite athletes were members of national teams, and they trained more than 10 hours per week. Masters were defined as athletes over 30 years of age who had been former national team members, were still participating in master championships and their amount of training was between 6 and 9 hours per week. Healthy volunteers not participating in competitive sports composed the control group recruited from employees of Semmelweis University, mainly medical students and residents. Their physical activity was less than 3–4 hours per week according to the questionnaire mentioned above. The upper limit of training time during Holter monitoring was maximum 2 hours. Individuals were excluded if they had any history of heart disease, diabetes, or still existing systemic disease.

3.1.2. Study Population of Exercise ECG Projects

Patients who underwent exercise treadmill testing between September 21, 1993, and December 20, 2010, were identified retrospectively using the Mayo Integrated Stress Center (MISC) database in Rochester, Minnesota, USA. This computerized database contains prospectively collected demographic and clinical information about patients.

For our exercise HR project we included patients aged 40 to 89 years who had performed non-imaging treadmill tests according to the Bruce protocol. Exclusion criteria to define our preliminary cohort were: (1) documented history of known CVD, including ischemic heart diseases, heart failure, cardiac surgery, structural or valvular heart diseases, major arrhythmias, defibrillator or pacemaker, congenital heart diseases, cerebrovascular

diseases, and peripheral vascular diseases; (2) use of any HR attenuating or rhythm-modifying agents, including beta blockers, calcium channel blockers, sotalol, and amiodarone, at the time of the exercise test; (3) patients younger than 40 years because reasons for exercise testing in younger patients were different and the number of younger patients was relatively small; (4) the test was not symptom limited but stopped because of ST changes, major arrhythmias, or abnormal BP response; and (5) for patients who underwent multiple exercise tests during the study period, only the initial exercise test was included.

For our smoking project the study population was basically the same, but we included patients older than 30 years and we did not exclude patients using HR attenuating or rhythm-modifying drugs.

Demographic and relevant clinical characteristics extracted from the database included hypertension (defined by previous diagnosis or receiving antihypertension medication), diabetes mellitus (defined by previous diagnosis), obesity (defined as body mass index of 30 kg/m^2), and current smoking. Smoking status was defined according to the Centers for Disease Control (CDC) definitions. (152) Never smokers have not smoked 100 cigarettes in their lifetime and do not smoke now. A smoker was considered past smoker if smoked at least 100 cigarettes but does not smoke any now. Current smokers have smoked at least 100 cigarettes in their lifetime and currently smoke. We also identified patients who were grossly unfit or unable to exercise adequately as having a FAC of < 80%. Patients were divided into 3 groups by smoking status, and then these groups were sub-divided into 3 groups according to CRF based on FAC on the exercise test: poor CRF < 80%, reduced CRF 80 – 99%, normal CRF ≥ 100%.

Ethical approval for the Hungarian research projects was obtained from the Central Ethics Committee of Hungary (13697- 1/2011-EKU[443/PI/11.]) and all participants gave informed consent. Exercise ECG investigations were a retrospective database studies approved by the Institutional Review Board of Mayo Clinic, Rochester, Minnesota. Subjects who did not consent to have their data used in research under Minnesota Statue (§144.335) were excluded. (153)

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3.2. Measurements

3.2.1. Athletes

Resting 12- lead ECG

Standard resting 12-lead ECGs were recorded (BTL – 08MT). Detailed ECG analysis was performed using the 2010 recommendations for ECG interpretation of athletes by the European Society of Cardiology. (96)

Holter ECG

Three-channel Holter ECG screening was applied (ScottCare Cardioview DxSuite, USA) using modified V5, V1 and III leads. (**Figure 12**)

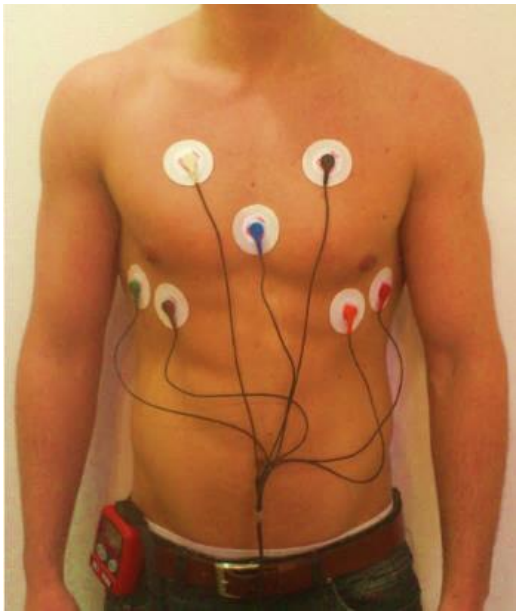

Figure 12. Electrode position of three-channel Holter ECG recording.

Automatic HRV analysis was carried out using software HolterCare ver. 10.2.2, 32 bit Windows 7 Enterprise, Service Pack 1 in the system DELL Optiplex 755 [Intel(R) Core(TM) 2 Duo CPU E 8400 @ 3.00 GHz 2.99 GHz, 2.00 GB]. After the automatic analysis, all recordings were examined by a physician to verify premature beats and artifacts. During the test the participants were asked to do their daily routine as usual, including training, food intake and sleeping.

Holter ECG Variables

Short- and long-term time-domain parameters were studied excluding premature and artifacts beat as follows: (1) The standard deviation of all normal-to-normal intervals (SDNN), which is a global index of HRV reflecting all circadian changes during the whole recording period. It characterizes the overall variability of HR, which means it can be influenced both by parasympathetic and sympathetic stimulation. (2) The mean of the 5-min standard deviation of the normal-to-normal intervals (SDNN Index), which measures the variability of 5-min cycles. It integrates the fast and intermediate components of HRV. (3) The square root of the mean squared differences between adjacent NN intervals (RMSSD) and (4) the percentage of successive normal-to-normal interval differences that are greater than 50 ms (pNN50) primarily reflects the parasympathetically mediated short-term alterations of autonomic tone (9).

3.2.2. Non-Athletes

Exercise Treadmill Test Protocol

Symptom-limited treadmill exercise testing was performed using the standard Bruce protocol according to the American College of Cardiology / American Heart Association guidelines. (154,155) Where multiple qualifying tests were available for a given patient, the first test chronologically was chosen to maximize follow-up. Symptoms, BP, HR, rating of perceived exertion (RPE), and workload were electronically entered into the database during the final minute of each stage of exercise, peak exercise, 1 and 3 minutes of active recovery, and 6 minutes after peak exercise in passive recovery. Tests were supervised by a certified exercise specialist or a cardiac nurse and interpreted by a cardiologist, who was immediately available for emergencies.

Exercise Treadmill Test Variables

Exercise data used in analyses included percentage of predicted FAC calculated from published equations from our laboratory with adjustment for age and sex. (137) Patients with an FAC of 80% were considered either grossly unfit or unable to exercise adequately to achieve peak HR. A positive exercise ECG was defined by standard criteria. An abnormal exercise ECG was defined as any test with 1.0 mm ST deviation irrespective of whether the resting ST segments were normal. Resting HR obtained in the standing

position and peak HR were identified and used to calculate the HR reserve (difference between peak and resting HR). The HR recovery was defined as peak HR minus HR at 1 minute of active recovery (1.7 miles per hour/0% grade) and was considered abnormal if it was less than 12 beats/min. (10)

Outcomes

Outcomes were taken from Mayo Clinic patient records and the Minnesota Death Index, which was reviewed in March, 2016. A death was considered to be CV-related if a CV condition was included among the first three listed causes in the Minnesota Death Index. CV mortality data was classified using International Classification of Diseases (ICD) 9 (391, 391.9, 394-398, 402, 404, 410-414, 415-417, 420-429, 430-438, 440-448, 451-454, 456-459) and ICD 10 (I101, I05-I09, I11, I13, I20-I25, I26-I28, I30-I52, I60-69, I70-I79, I80-89) codes. Cancer death was also defined by ICD 9 (173, 235-239, 273, 569, 602, 622-624) and ICD 10 (C00-C26, C30-C41, C43-C58, C60-C80, C7A, C7B, C81-C96) codes.

3.3. *Statistical analyses*

Athletes (Research Aims 1-2)

Statistical analyses were performed using SPSS 15.0 program package.

Age was compared using two-sample t-test, while gender and ECG characteristics were compared using Fisher's exact test. Differences between groups were evaluated using one-way analysis of variance (ANOVA) (grouping variable: either sport intensity or kind of sport activity; dependent variable: age or recording time), while gender distributions were compared using Fisher's exact test (rows: pairs of either sport intensity or kind of sport activity, columns: gender). Differences between HRV parameters of the studied groups were assessed after normalizing square-root transformation by analysis of covariance (ANCOVA) with age as a covariate (grouping variable: either sport intensity or kind of sport activity, dependent variable one of HRV parameters). Pairwise comparisons of age-corrected means were performed using Tukey–Kramer post hoc test. For significant differences shown in text effect sizes (e.s.) are also presented. Data are expressed as mean ± standard deviation (SD) or, categorical data are presented as

percentages; in case of square-root transformed data, back-transformed (squared) mean and confidence interval (CI). Normal distribution curves were fitted by square root transformation, and lower cut-off values were determined at 5 %.

Non-Athletes (Research Aims 3-4)

For the exercise testing data, statistical analyses were carried out using SAS Studio Version 5. Statistical analyses proceeded in 2 parts: (1) create a preliminary cohort of patients without CVD or drugs affecting HR and identify the comorbidities that influence peak HR and (2) determine the relationship between exercise HR and sex in a pure cohort with those comorbidities eliminated. Baseline characteristics and exercise test variables in the preliminary cohort were compared by sex using 2-sided t tests for continuous variables and the chi-square test of continuity for categorical variables. Analysis of variance using the general linear model was used to identify factors affecting peak HR with adjustment for sex and age. Factors included in the model were diabetes, hypertension, hyperlipidemia, obesity, and unfit status (FAC< 50%).

Patient characteristics, outcomes, and exercise data were also analyzed by smoking status. Differences among continuous variables were assessed by analysis of variance under the general linear model (SAS PROC GLM) with multiple comparisons handled by Tukey's method, while logistic regression (SAS PROC LOGISTIC) was used to determine differences in discrete variables according to smoking status. For the primary analysis of smoking-related comorbidities diabetes, hypertension, and obesity, logistic regression models were adjusted for age and sex. Differences among smoking groups in total, CV, and cancer death were tested using Cox proportional hazards regression (SAS PROC PHREG) with adjustment for age, sex, and the 3 smoking-related comorbidities. Finally, we also analyzed mortality by smoking status and level of CRF. Never smokers with normal CRF formed the referent group, then the differences between hazard ratios were tested within the groups with the reference of normal CRF never, past and current smokers.

$P < .05$ was considered significant for all analyses.

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4. Results

4.1. Electrocardiographic Findings

4.1.1. Study Population

Standard ECG screening was applied in 227 Caucasian athletes (male: 180, age: 27.2 ± 8.7). Elite athletes (n = 155) including several members of the Hungarian Olympic team, masters (n = 16), non-elite athletes (n = 56) and 89 controls (male: 57, age: 28.1 ± 6.8) were examined. No difference was found in age between athletes and controls, but the rate of female gender was higher in controls. Athletes performed various sports, mainly kayaking and canoeing, water polo and rowing. They were in diverse phases of training, with 51.5% in training period, 13.2% in speed up period and 10% competing.

4.1.2. Training-related Physiological ECG Findings

According to our results, almost all athlete had at least one training-related ECG sign. Sinus bradycardia, early repolarization and isolated voltage criteria of LVH were common and found more often in athletes compared to the control group (**Table 2, Figure 13**). Incomplete right bundle branch block and 1st degree AV block were often seen as well, but no differences were found between groups. Marked sinus arrhythmia and transient junctional rhythm also appeared in some athletes and controls (**Figure 14**).

Table 2. Incidence of physiological, training related ECG changes.

ECG findings	Athletes		Controls	
	N	%	N	%
Sinus bradycardia	116	51.1**	12	13.5
Early repolarization	146	64.3**	32	35.9
Left ventricular hypertrophy[×]	52	22.9**	7	7.8
Incomplete right bundle branch block	70	30.8	28	31.5
1st degree AV block	25	11.0	6	6.7
Junctional rhythm	2	0.9	1	1.1

([×] isolated voltage criteria) ** P < .005 versus controls

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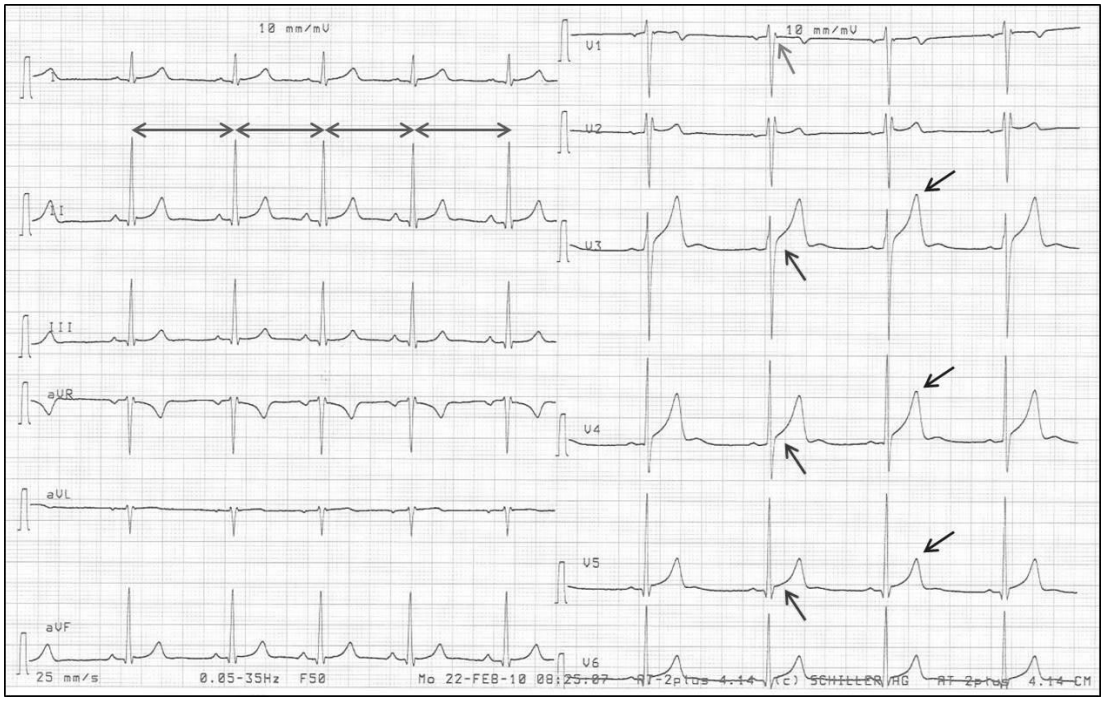

Figure 13. A characteristic athletic ECG of a 23-year old elite male rower. Sinus bradycardia (mean heart rate: 57/min), sinus arrhythmia (horizontal arrows), incomplete right bundle branch block (lighter upsloping arrow), early repolarization in V3–V5 leads (darker upsloping arrow) and vagotonic T-waves (downsloping arrows)

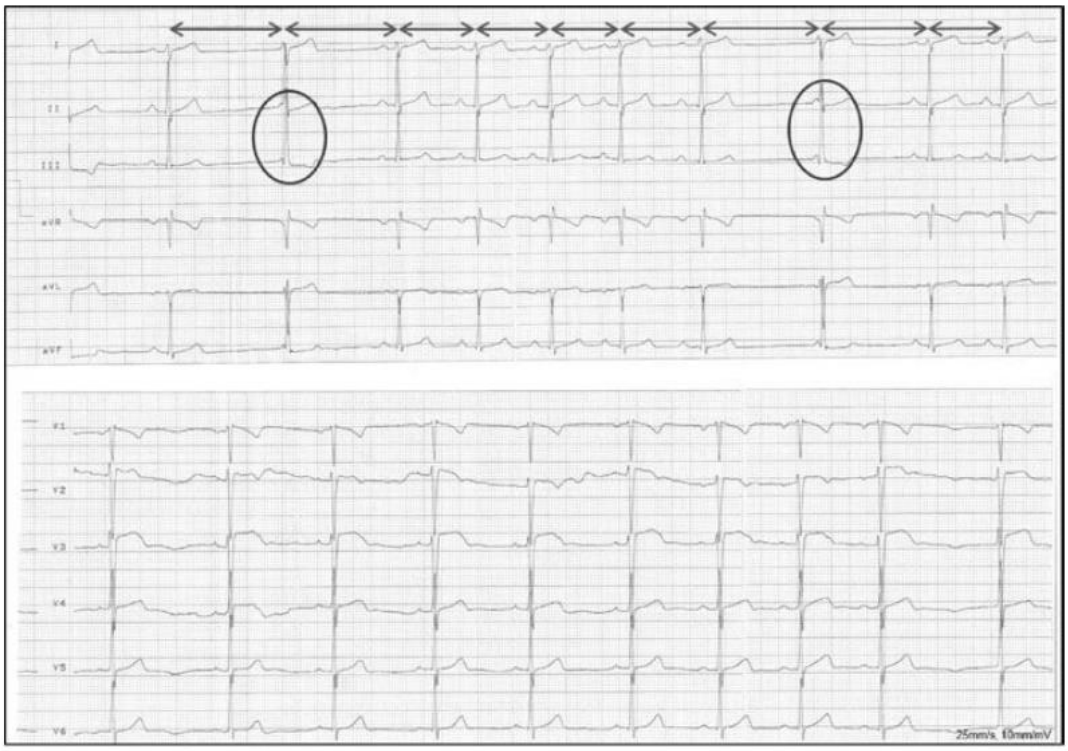

Figure 14. Resting ECG recording of a 24-year old elite female water polo player. Marked sinus arrhythmia with visible variability of RR intervals (arrows). Junctional beats (circles) follow longer pauses mimicking AV-node disease. Marked, 2–3 mm early repolarization in V3 lead.

4.1.3. Training-unrelated Pathological ECG Findings

Some ECG signs considered pathological such as repolarization changes including T-wave abnormalities, ST-segment changes and signs of pathological LVH were found more often in athletes compared to the control group (**Table 3**). In 15% of the athletes, we recorded T-wave inversion classified as pathological. In most cases, T-wave inversion occurred in adjacent inferior or V1–V3 leads. Out of the ST-segment changes considered training unrelated, about half were ≥ 1 mm horizontal or down-sloping ST-depression in inferior, lateral or precordial leads, some were 1–3.5 mm descending or horizontal ST-elevation in V1–V4 leads, few were 1–2 mm horizontal, flat ST-segment elevation in inferior leads. LVH considered pathological – mostly associated with T-wave inversion – was presented in more than 5% of the athletes while in no controls (**Figure 15**). Signs of RVH, atrial enlargement and conduction abnormalities were rare either in athletes or controls with no difference between groups. Left posterior hemiblock, left and right bundle branch blocks were found in some athletes while these appeared in no controls (**Table 3**). We found complete right bundle branch block (CRBBB, QRS: 120 msec) in one 22 year old elite male rower and complete left bundle branch block (CLBBB, QRS: 160 msec) in one 16 year old non-elite male scrapper. ECG recordings of a 24 year old elite male canoeist and a 37 year old triathlon athlete raised the possibility of preexcitation syndromes (**Figure 16**)

All athletes who had any pathological ECG abnormality underwent our detailed cardiology exam including echocardiography and cardiac MR. We did not find any stuctural heart disease, therefore no athlete was disqualified.

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Table 3. Incidence of pathological, training-unrelated ECG changes.

ECG findings	Athletes		Controls	
	N	%	N	%
T-wave changes	34	15.0*	5	5.6
ST- segment changes	15	6.6*	1	1.1
Pathological left ventricular hypertrophy	12	5.3*	-	-
Right ventricular hypertrophy	6	2.6	1	1.1
Atrial hypertrophy	6	2.6	1	1.1
Left anterior hemiblock	5	2.2	1	1.1
Left posterior hemiblock	3	1.3	-	-
Delta-wave	2	0.8	-	-
Left bundle branch block	1	0.4	-	-
Right bundle branch block	1	0.4	-	-

* P < .05 versus controls

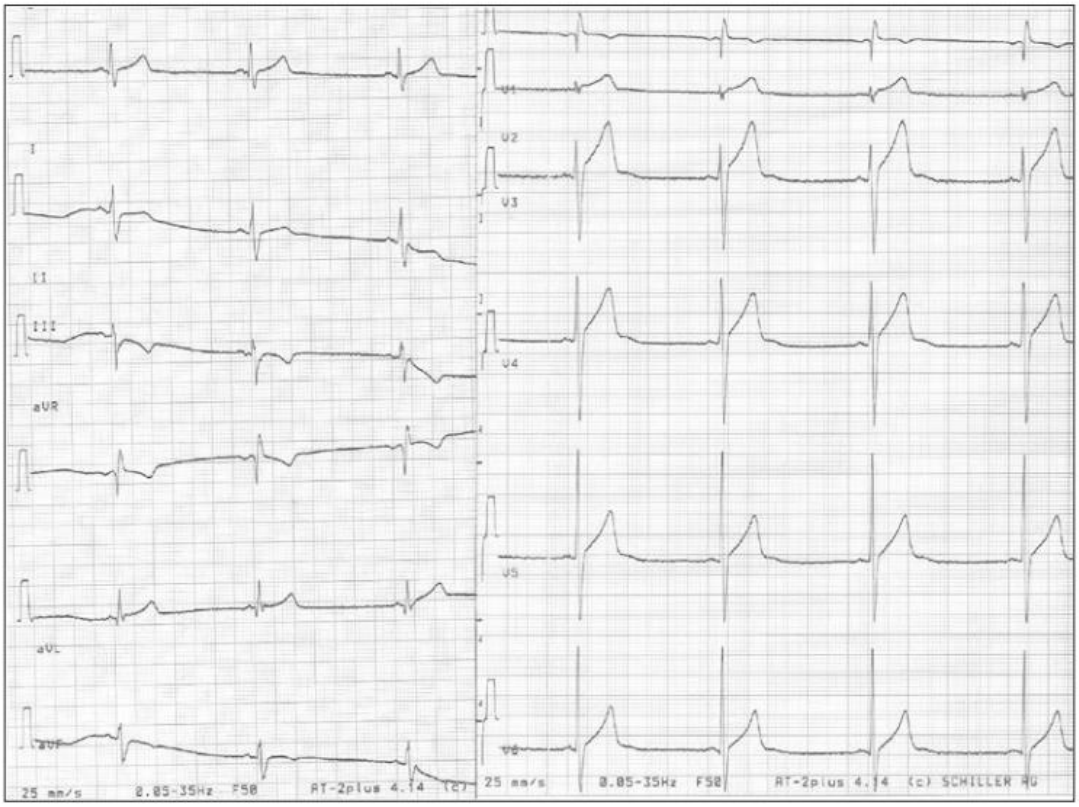

Figure 15. Left ventricular hypertrophy considered pathological in an asymptomatic 31 year old elite male rower. Marked sinus bradycardia (mean heart rate: 43/min), incomplete right bundle branch block, early repolarization and vagotonic T-waves in precordial leads. Cornell-criteria of left ventricular hypertrophy (S in V3 and R in aVL ≥ 20 mm) and 1–3 mm T-wave inversion in leads III and aVF

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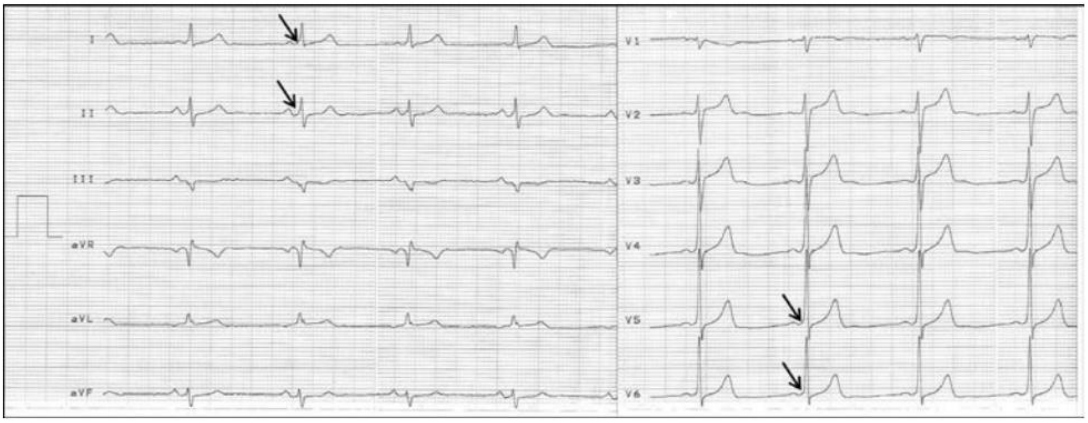

Figure 16. Sinus bradycardia (mean heart rate: 58/min). Delta waves appearing in inferior and lateral leads (arrows), causing slightly widened QRS komplexes (110 msec) and shortened AV-conduction (PQ: 100 msec) on the ECG recording of a 24 year old elite male canoeist (arrows)

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4.2. Holter ECG Findings

4.2.1. Analysis by Study Group

The Holter ECG screening was applied in 138 athletes (male 110, age 28.4 ± 8.3, recording time 21.3 ± 3.0 h) and 100 healthy controls. Characteristics of the study groups are given in **Table 4**. No difference was found in recording time among the studied groups. Masters athletes were older than all the other groups by study design. The ratio of males was higher in all the athlete groups compared to the controls (**Table 4**). All studied short- and long-term time-domain parameters of HRV were higher in elite athletes compared to controls [SDNN (CI) 225.3 (216.2–234.5) versus 158.6 (150.2–167.1) ms (e.s.:1.43); SDNN Index (CI) 99.6 (95.6–103.7) versus 72.4 (68.7–76.2) ms (e.s.:1.32); pNN50 (CI) 24.2 (22.2–26.3) versus 14.4 (12.7–16.3) % (e.s.: 0.96); RMSSD (CI) 71.8 (67.6–76.2) versus 50.8 (46.9–54.8) ms (e.s.:0.96); p<0.001] (**Figure 17**). All studied HRV parameters of masters were higher than controls. No difference could be found between HRV values of elite athletes and masters. No effect of gender on the studied HRV parameters could be established.

Table 4. The studied groups

	N	Age ± SD (year)	Male/female	Recording time ± SD (h)
Elite athletes	121	26.7 ± 7.1[#]	94/27*****	21.2 ± 3.1
Masters	17	40.0 ± 6.8	16/1*****	21.9 ± 2.1
Controls	100	28.3 ± 6.9[#]	57/43	22.0 ± 2.4

[#] P < .001 versus masters, * P < .01 versus controls

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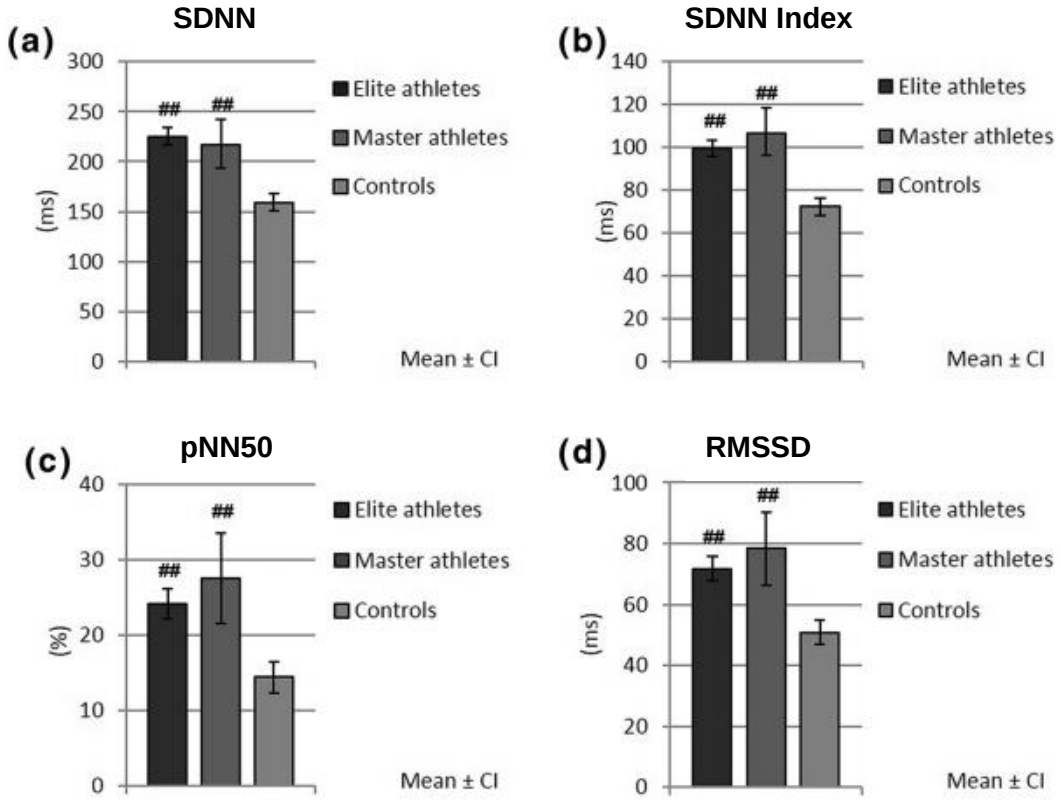

Figure 17. HRV analysis in elite athletes, masters athletes and controls. a SDNN, b SDNN Index, c pNN50 (%), and d RMSSD. (SDNN standard deviation of normal-to-normal intervals, SDNN Index the mean of all the 5-min standard deviations of normal-to-normal intervals during the 24-h period, pNN50 the percentage of differences between successive normal-to-normal intervals over 24 h that are greater than 50 ms, RMSSD the root mean square successive difference.)
P < .001 versus control

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4.2.2. Analysis by Sport

Athletes were classified into six sport groups, as identified in **Figure 18**. Subgroup analysis by sport activities was carried out in cyclists + triathlonists, canoe and kayak paddlers, waterpolo players, rowers, runners and combat fighters (kick-boxers and thai boxers) (**Table 5**). Runners were older than all other studied sport groups as most of them were ultramarathon runners. The ratio of females was higher in the waterpolo group compared to canoe and kayak paddlers, rowers and cyclists + triathlonists. All studied age-corrected HRV parameters were the highest in canoe and kayak paddlers and cyclists + triathlonists and the lowest in runners (**Figure 19**). Canoe and kayak paddlers had higher SDNN index: 110.0 (103.1–117.2) versus 81.6 (71.0–92.9) ms (e.s.:1.33), pNN50: 27.7 (24.2–31.4) versus 17.2 (12.5–22.7) ms (e.s.:1.00), and RMSSD values: 81.9 (74.1–88.1) versus 54.4 (42.3–63.7) ms (e.s.:1.15), cyclists + triathlonists had higher SDNN index value than runners 103.8 (94.2–114.0) versus 81.6 (71.0–92.9) ms (e.s.:1.05).

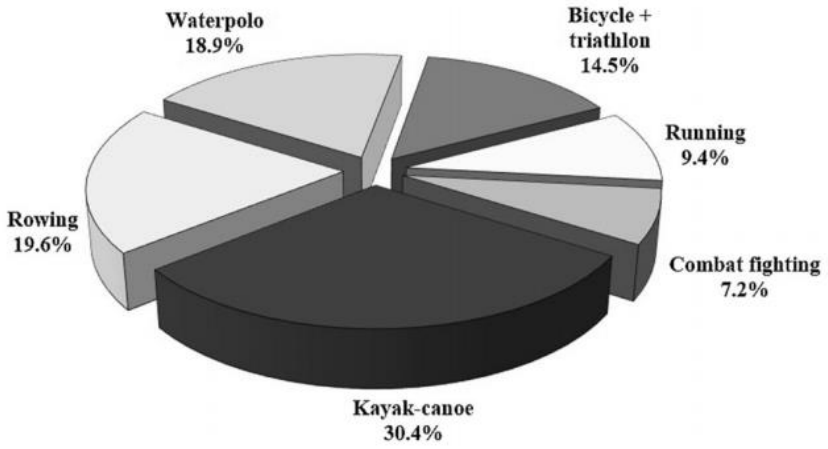

Figure 18. Sports of the studied athletes.

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Table 5. Subgroup analysis by sport activity: the studied groups

	N	Age ± SD (year)	Male/female	Recording time ± SD (h)
Kayak-canoe	42	28.7 ± 9.4*	37/5≠	21.6 ± 2.5
Rowing	27	24.6 ± 6.5*	22/5≠	20.9 ± 4.1
Waterpolo	26	28.7 ± 6.0*	14/12	21.0 ± 3.0
Bicycle + triathlon	20	29.1 ± 8.4*	18/2≠	21.8 ± 1.7
Running	13	37.9 ± 5.0	10/3	21.3 ± 2.2
Combat fighting	10	22.2 ± 4.7*	9/1	20.5 ± 4.4

* P < .05 versus running, ≠ P <. 05 versus waterpolo

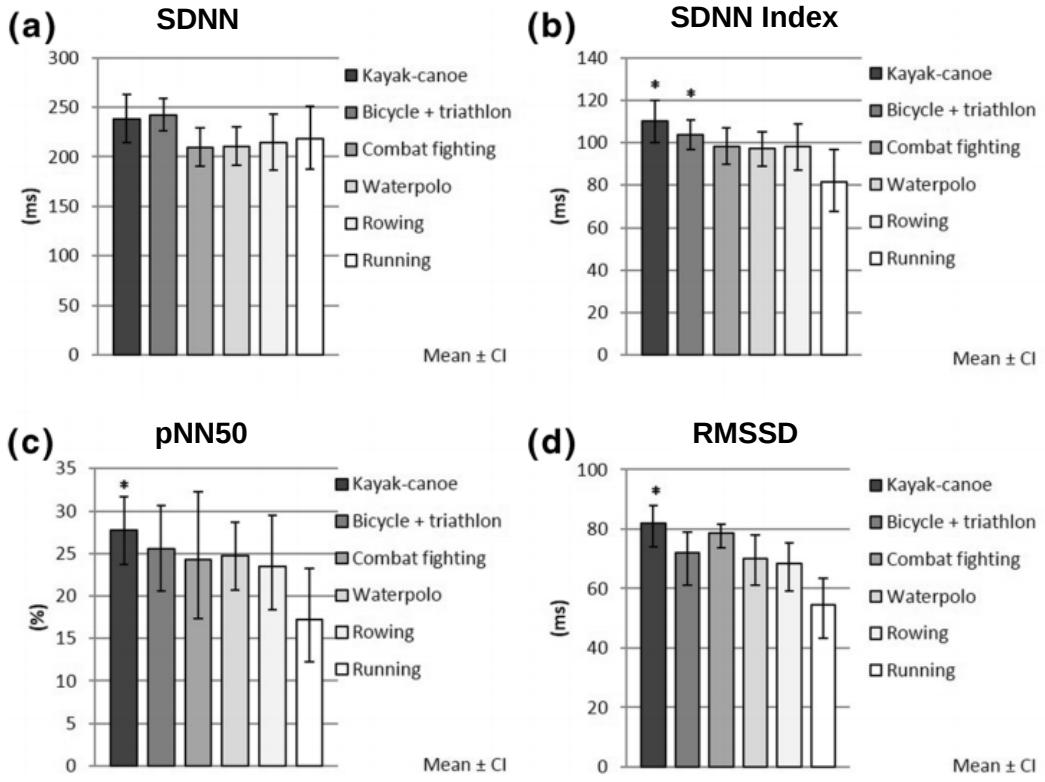

Figure 19. Subgroup analysis by sport activities. a SDNN, b SDNN Index, c pNN50 (%), and d RMSSD. (SDNN standard deviation of normal-to-normal intervals, SDNN Index the mean of all the 5-min standard deviations of normal-to-normal intervals during the 24-h period, pNN50 the percentage of differences between successive normal-to-normal intervals over 24 h that are greater than 50 ms, RMSSD the root mean square successive difference.) * P < .05 versus running

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4.2.3. Sample individual HRV analyses

Figure 20 shows representative individual recordings of HRV analysis demonstrating the duration of sinus RR intervals compared to the preceding RR intervals in four individuals under different intensity training. The RR variability visibly rises with the intensity of training, which is highest in elite athletes. As compared to the recommended normal values, the HRV parameters of all studied persons fell into the normal ranges. (156)

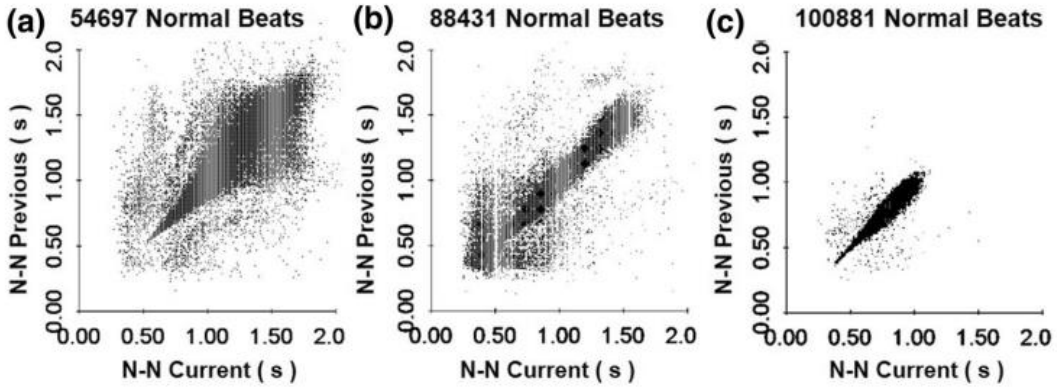

Figure 20. Duration of sinus RR intervals compared to the preceding RR intervals during the recorded period. Representative diagrams of RR variability in individuals under different intensity training. a Elite athlete No. 129, b master No. 2, c control No. 57

4.2.4. Comparison of Lower Cut-off Values

In the controls, the 5 % lower cut-off values were comparable to the published normal values (SDNN: 97.6 ms, SDNN Index 44.1 ms, pNN50 2.6 %, RMSSD 24.6 ms). On the contrary, the normal distribution curves of all studied HRV parameters shifted to the right with substantially higher cut-off values in elite athletes (SDNN 147.4 ms, SDNN Index 66.6 ms, pNN50 9.7 %, RMSSD 37.9 ms (**Figure 21**).

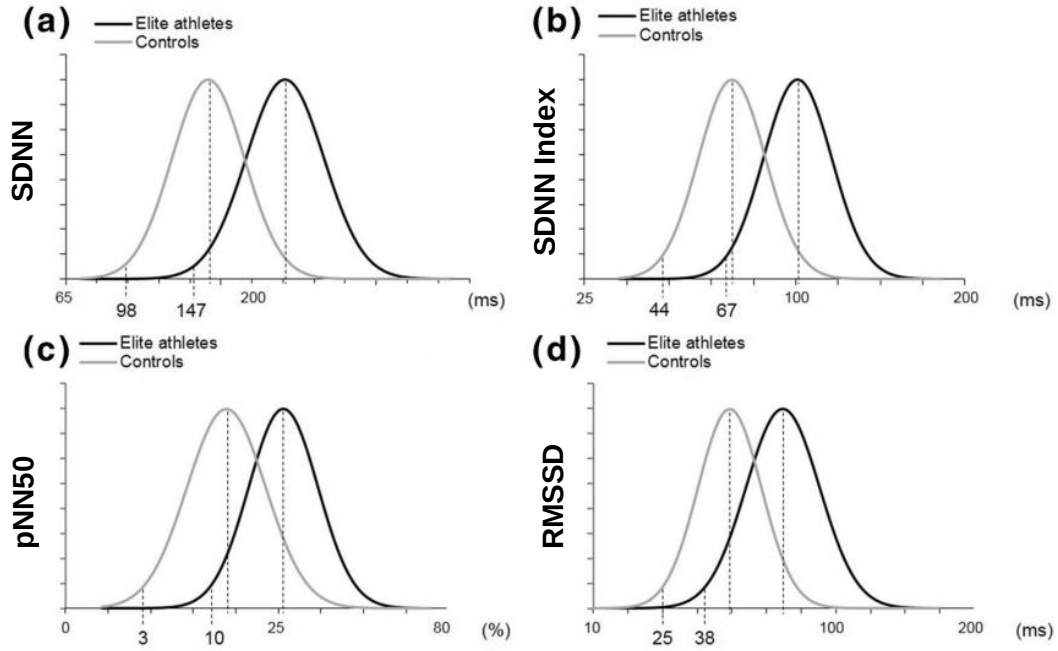

Figure 21. Normal distribution curves and lower cut-off values of elite athletes and controls. a SDNN, b SDNN Index, c pNN50 (%), and d RMSSD. (SDNN standard deviation of normal-to-normal intervals, SDNN Index the mean of all the 5-min standard deviations of normal-to-normal intervals during the 24-h period, pNN50 the percentage of differences between successive normal-tonormal intervals over 24 h that are greater than 50 ms, RMSSD the root mean square successive difference.)

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4.3. Exercise Test Results

4.3.1. Study Population

Our cohort was derived from adults consecutively referred for exercise stress testing at Mayo Clinic, Rochester, between September 21, 1993, and December 20, 2010. We initially reviewed 105,220 exercise tests on 79,769 unique patients. Of these, 37,010 met preliminary inclusion and exclusion criteria as described in **Figure 22**. Clinical characteristics of the preliminary cohort are presented according to sex in **Table 6**. Approximately 90% were white, 3% African American, and 7% another race. The low prevalence of hypertension was likely explained by the exclusion for HR attenuating drugs. In general, the risk factor burden was low, consistent with the sociodemographic characteristics of the cohort and the exclusion for CVD.

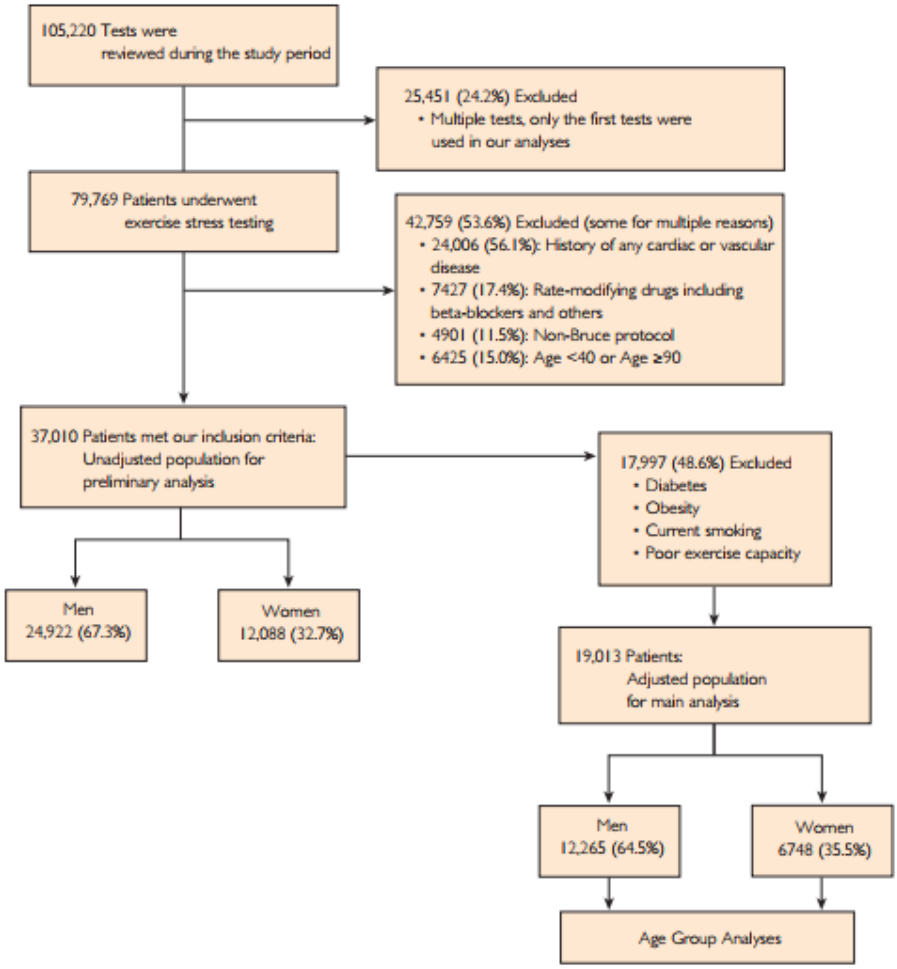

Figure 22. Flowchart of the study population (September 1993 - December 2010) for heart rate responses in men and women.

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Table 6. Baseline characteristics in men vs women in the preliminary clinical cohort

	Men (n=24,922)	**Women (n=12,088)**	**P**
Age (years)	54 ± 9	55 ± 9	<.001
Hypertension (%)	18	16	<.001
Diabetes (%)	6	4	<.001
Body Mass Index (kg/m^2)	29 ± 5	27 ± 6	<.001
Obesity (%)	35	28	<.001
Current Smoking (%)	10	9	.002
Unfit physical status (%)	19	21	.002

Continuous data are presented mean ± SD, categorical data as percentage of sample.

For the smoking analyses, after applying our exclusion criteria – exclusion of multiple tests (n=21,687); non-Minnesota residents (n=45,885); patients with history of baseline CVD (n=9,173); patients younger than 30 years old (n=1,304) and those patients whose smoking data was incomplete (n=1,425) – the final cohort included 21,981 patients **(Figure 23)**.

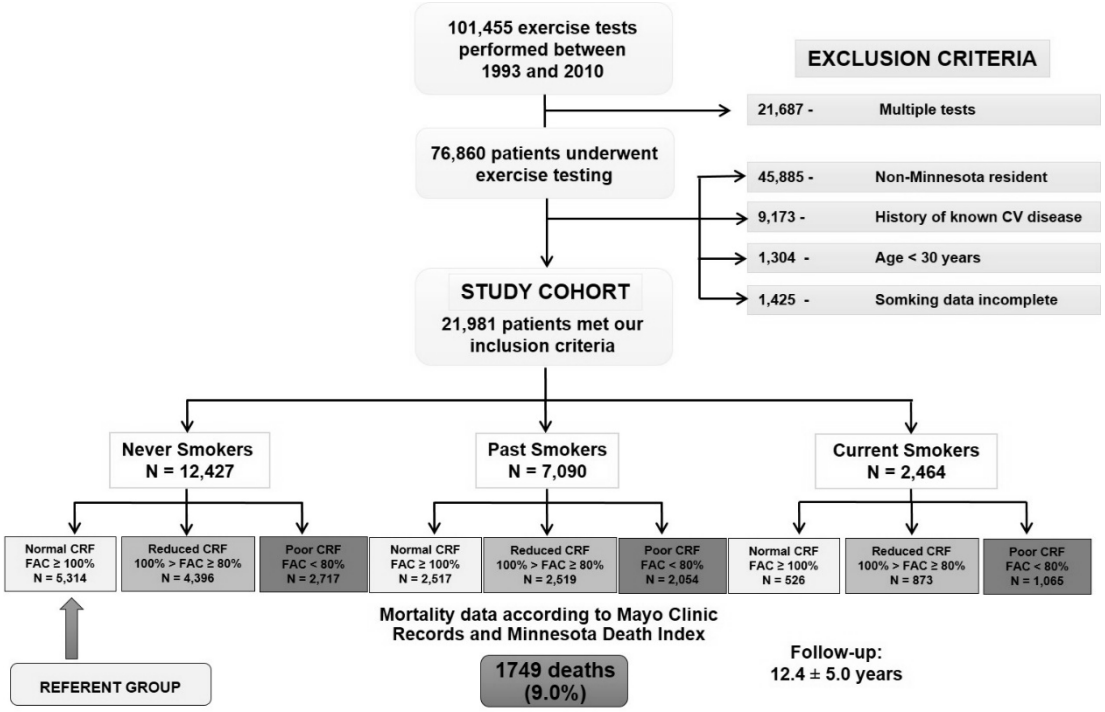

Figure 23. Flowchart of the study population (September 1993 - December 2010) for the smoking project.

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Their demographic and clinical data by smoking status (never, past and current smokers) are provided in **Table 7**, along with the long-term outcome data.

Table 7. Baseline characteristics by smoking status.

	Never Smokers N = 12,427	**Past Smokers N = 7,090**	**Current Smokers N = 2,464**
Age (years)	50.9 ± 11.1^{2}	54.3 ± 10.8^{3}	48.2 ± 9.5^{1}
Female (%)	$4833\ (38.9)^{2}$	$2315\ (32.7)^{1}$	$827\ (33.6)^{1}$
Hypertension (%)	$2764\ (22.2)^{1}$	$1968\ (27.8)^{2}$	$500\ (20.3)^{1}$
Diabetes (%)	$664\ (5.3)^{1}$	$533\ (7.5)^{2}$	$137\ (5.6)^{1}$
Body Mass Index (BMI, kg/m^2)	28.7 ± 5.6^{1}	29.3 ± 5.5^{2}	28.7 ± 5.8^{1}
Obesity (BMI ≥ 30, %)	$4401\ (35.4)^{1}$	$2853\ (40.2)^{2}$	$920\ (37.4)^{1}$
All-cause mortality (%)	$771\ (6.2)^{1}$	$750\ (10.6)^{3}$	$228\ (9.3)^{2}$
CV mortality (%)	$256\ (2.1)^{1}$	$279\ (3.9)^{3}$	$83\ (3.4)^{2}$
Cancer mortality (%)	$340\ (2.7)^{1}$	$352\ (5.0)^{3}$	$105\ (4.3)^{2}$

Continuous data are presented mean ± SD; categorical data as number (percentage of sample). BMI = Body Mass Index.

Different superscript numbers indicate a statistically significant difference between groups at P <.05.

Past smokers were older, less likely female, and had significantly more obesity, hypertension, and diabetes compared to never smokers. Current smokers did not show an increased prevalence of obesity, hypertension, and diabetes compared to never smokers but had much higher rates of poor CRF. Comorbidity and mortality rates in **Table 7** – which are highest in past smokers – are not age and sex-adjusted.

4.3.2. General Exercise Test Results

Exercise test results are given in **Table 8**. Performance time was greater for men than for women, as expected. The FAC was near 100% for both sexes because we used our own laboratory standards for the FAC. (137) All tests were symptom limited; peak rating of perceived exertion averaged approximately 18 on the 6-20 Borg Scale. (157) Resting HR was higher for women than for men, but other HR parameters and BP parameters were higher for men than for women. Positive exercise ECG was slightly more common in men than in women, with no difference in the frequency of abnormal exercise ECG (includes all tests with 1 mm ST depression regardless of resting ST-T abnormalities). Note that the large sample size meant that very small, probably nonphysiological differences were nonetheless statistically significant.

Table 8. Exercise test parameters in men vs women in the preliminary clinical cohort.

Exercise test parameters	**Men (n=24,922)**	**Women (n=12,088)**	**P**
Exercise time (min)	9.8 ± 2.3	7.6 ± 2.0	<.001
FAC (%)	97 ± 21	99 ± 24	<.001
Resting HR (bpm)	76 ± 13	80 ± 12	<.001
Percent predicted peak HR traditional (%)	100 ± 9	99 ± 9	<.001
Peak HR (bpm)	166 ± 17	163 ± 16	<.001
HR recovery (bpm)	19 ± 8	18 ± 9	.03
HR reserve (bpm)	90 ± 19	84 ± 17	<.001
Resting systolic BP (mmHg)	125 ± 17	120 ± 18	<.001
Resting diastolic BP (mmHg)	81 ± 11	77 ± 11	<.001
Peak systolic BP (mmHg)	184 ± 24	168 ± 24	<.001
Peak diastolic BP (mmHg)	78 ± 16	75 ± 16	.001
Peak RPE	18 ± 1	18 ± 1	.03
Abnormal ECG (%)	9	8	.07
Positive ECG (%)	5	4	<.001

Continuous data are presented mean ± SD, categorical data as percentage of sample.
Abbreviations: FAC = functional aerobic capacity; HR = heart rate; BP = blood pressure; RPE = rating of perceived exertion; ECG = electrocardiogram

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Table 9 provides the exercise test results by smoking status for the whole cohort of 21,981 patients.

Table 9. Exercise test results by smoking status.

Exercise test parameters	Never Smokers N = 12,427	Past Smokers N = 7,090	Current Smokers N = 2,464
FAC (FAC, %)	96.0 ± 21.9[1]	91.8 ± 22.4[2]	83.6 ± 21.2[3]
Normal CRF (FAC >100%, %)	5314 (42.8)[1]	2517 (35.5)[2]	526 (21.4)[3]
Reduced CRF (100 > FAC ≥ 80%, %)	4396 (35.4)[1]	2519 (35.5)[1]	873 (35.4)[1]
Poor CRF (FAC < 80%, %)	2717 (21.9)[1]	2054 (29.0)[2]	1065 (43.2)[3]
Resting HR (bpm)	76.9 ± 13.0[2]	76.3 ± 13.0[1]	77.9 ± 12.9[3]
Peak exercise HR (bpm)	165.7 ± 19.0[1]	159.7 ± 20.4[2]	158.2 ± 20.3[3]
Percent predicted peak HR (%)	97.8 ± 9.5[1]	96.2 ± 10.6[2]	92.1 ± 10.9[3]
Peak HR < 85% predicted	1157 (9.3)[1]	980 (13.9)[2]	566 (23.0)[3]
Taking beta-blockers (%)	1087 (8.8)[1]	731 (10.3)[2]	224 (9.1)[1,2]
HR recovery	19.3 ± 8.9[1]	17.7 ± 8.7[2]	16.8 ± 8.6[3]
HR recovery < 13 bpm	2583 (20.8)[1]	1915 (27.0)[2]	734 (29.8)[3]
Resting systolic BP (mmHg)	123.1 ± 17.6[2]	125.8 ± 18.2[3]	121.5 ± 17.2[1]
Resting diastolic BP (mmHg)	79.7 ± 11.0[2]	80.3 ± 11.2[2]	78.8 ± 11.6[1]
Peak systolic BP (mmHg)	175.5 ± 24.7[1]	179.2 ± 25.9[2]	174.8 ± 27.0[1]
Peak diastolic BP (mmHg)	75.2 ± 16.3[1]	78.1 ± 15.5[3]	76.8 ± 15.9[2]
Highest RPE	18.1 ± 0.8[1]	18.1 ± 1.0[1]	18.1 ± 0.9[1]
Positive exercise ECG	521 (4.2)[1]	436 (6.2)[2]	73 (3.0)[1]
Abnormal exercise ECG	959 (7.7)[1]	710 (10.0)[2]	136 (5.5)[1]

Continuous data are presented mean ± SD; categorical data as number (percentage of sample). Abbreviations: FAC = functional aerobic capacity, CRF = cardiorespiratory fitness, HR = heart rate, BP = blood pressure, RPE = rating of perceived exertion, ECG = electrocardiogram.

Functional aerobic capacity (FAC) defined as 100% x actual time/predicted time for age and sex. Rating of perceived exertion (RPE) measured on standard Borg Scale (6 – 20). Positive exercise electrocardiogram (ECG) defined by standard methods. Abnormal exercise electrocardiogram (ECG) defined as positive or abnormal but not diagnostic due to resting ST-T abnormalities.

Different superscript numbers indicate a statistically significant difference between groups at $P < .05$.

Because of the large sample size, even minor differences, such as HR and BP parameters may reach statistical significance, but some differences compared to never smokers were quite pronounced. There are significant trends towards decreasing CRF with smoking status. Current smokers in particular show lower CRF, less vigorous HR response, and more abnormal HR recovery than the never smokers. In general, past smokers were intermediate in all these variables. Among current smokers, more than 40% of the patients had poor CRF versus approximately 22% among never smokers. The prevalence of positive or abnormal exercise ECGs was relatively low in all three groups.

4.3.3. Peak Heart Rate by Age in Men versus Women in the Preliminary Clinical Cohort

To further examine the relationship between peak HR and age in men versus women, we separately plotted peak HR by age for men and women in the preliminary cohort of 37,010 patients (**Figures 24, A and B**). Using linear regression, lines predicting peak HR by age are shown in **Figure 24**, along with 90% CIs and the traditional line depicting 220 minus age. Note a large variance around the regression line in both sexes. The regression line more closely approximated 220 minus age in terms of both intercept and slope for men versus women.

4.3.4. Analysis of Factors Affecting Peak Heart Rate

Using multivariate regression on the preliminary cohort, comorbidities significantly affecting peak HR included poor exercise capacity (beta coefficient = - 11 beats/min), current smoking (-6 bpm), diabetes (-3 bpm), and obesity (-2 bpm). We excluded patients with these comorbidities to form the pure cohort of 19,013 patients (51.3% of full cohort). Peak HR was again plotted against age for men and women separately in **Figures 24, C and D**. The distribution of peak HR by age became tighter (with improved R^2) after eliminating patients with modifying risk factors, and the regression lines more closely approximated the traditional 220 minus age formula. For men, the regression line in our pure cohort was peak HR = 221 - 0.95 x age. For women, it was peak HR = 210 - 0.79 x age, which was still substantially different from the traditional 220 minus age formula. Comparing the relationship of peak HR to age between men with women in our pure cohort, both the regression slopes and intercepts were different at P<.0001.

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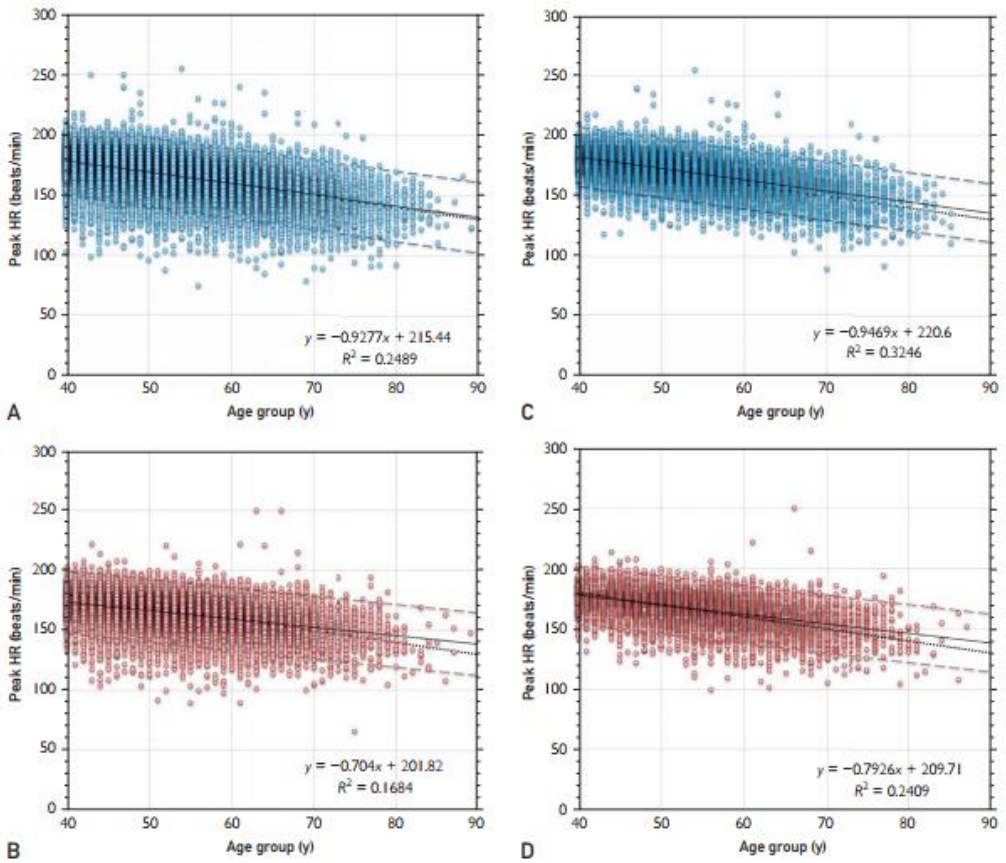

Figure 24. Scatter plot diagrams of the peak heart rate on the preliminary, unadjusted clinical cohort by age in men (A) and women (B), and on the final, adjusted clinical cohort in men (C) and women (D). Results of linear regression are shown as continuous lines, with 90% confidence intrevals shown as broken lines, whereas the traditional formula of 220 minus age is shown as dotted lines.

4.3.5. Exercise Test Parameters by Age in Men versus Women in the Pure Clinical Cohort

We divided the final data set into 5 age groups to analyze the effect of aging on HR parameters in men and women. All exercise HR parameters showed an inverse linear relationship to age in both sexes (**Figure 25**). Resting HR was higher in women than in men in all age groups. The HR reserve was lower in women than in men and showed continuously decreasing differences by successive age groups. In the 40 to 49 and 50 to 59 years age groups, significant differences were found in peak HR, but the curves crossed at the 60 to 69 years age group, and so older women had slightly higher peak HR than did men. Differences in HR recovery were small on comparing men and women, with a significant difference only in the age group 50 to 59 years.

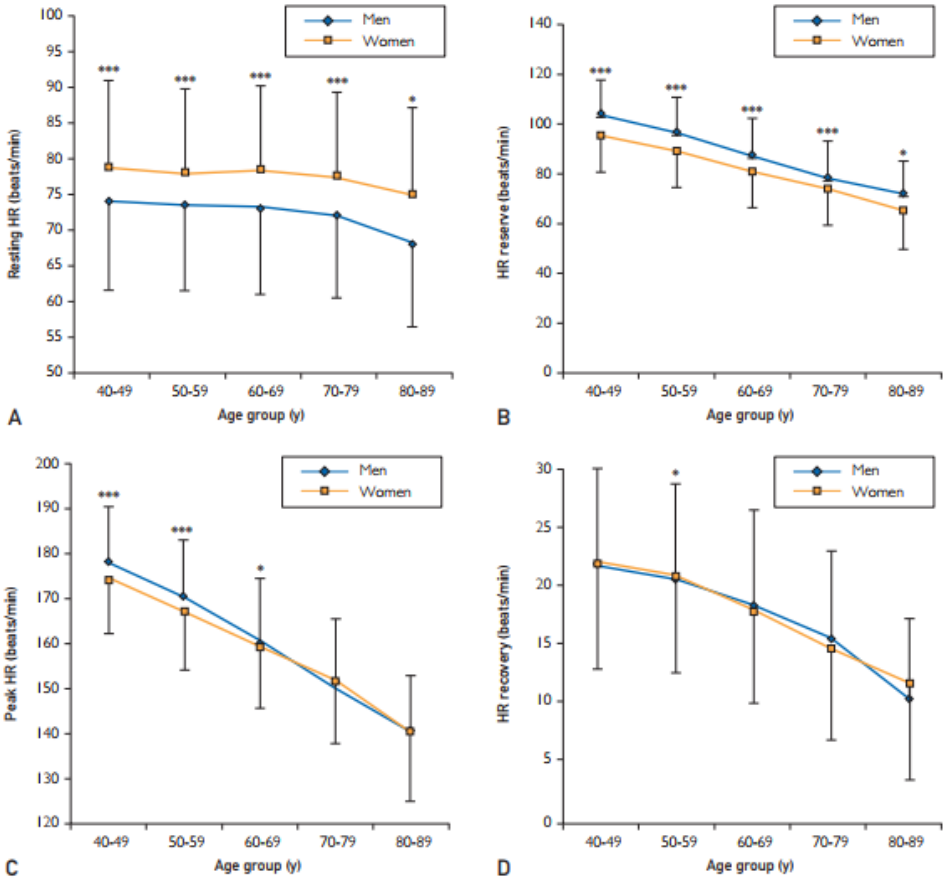

Figure 25. Resting HR (A), HR reserve (B), peak HR (C), and HR recovery (D) by age in men versus women in the final cohort. Data points represent mean ± SD. HR = heart rate. Significance levels: *** P < .05, * P < .05.

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4.3.6. Exercise Testing and Mortality Risk

Comorbidities by Smoking Status

For the next step of the analysis, logistic regression with age and sex adjustment was applied on comorbidities by smoking status to determine the risk of the presence of diabetes, obesity and hypertension according to smoking status. The results are shown on **Figure 26**. Past smokers had a greater prevalence of obesity, hypertension, and diabetes compared to never smokers. Current smokers did not show an increased prevalence of these comorbidities compared to never smokers.

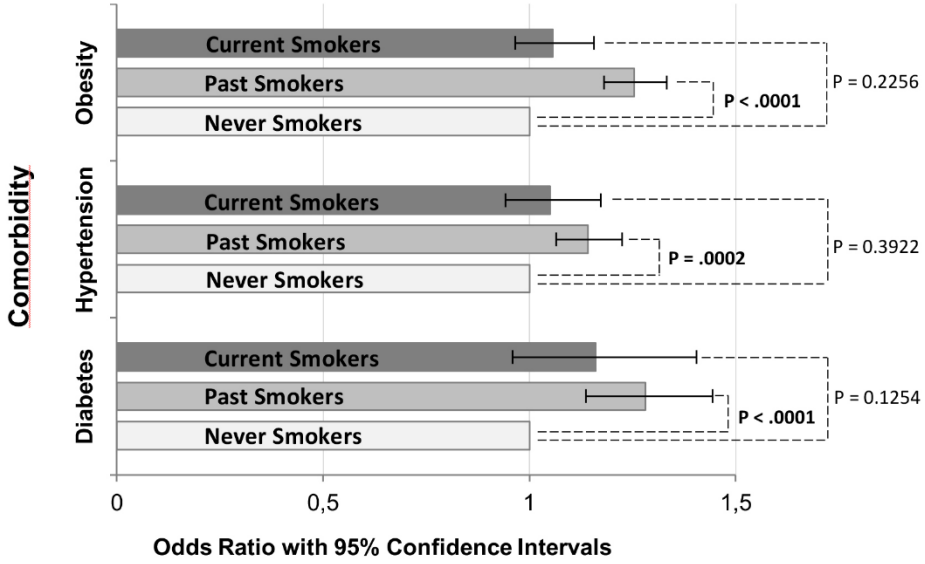

Figure 26. Odds ratios with 95% confidence intervals for comorbidities adjusted for age and sex. Never smokers was the referent group. P values indicate significance of the hazard ratios compared to never smokers.

Outcomes

There were 1749 deaths (9.0 %) over a mean follow-up of 12.4 ± 5.0 years. Consistent with exclusion of baseline CVD and residence in a state (Minnesota) with overall low CV death rates, cancer death was actually more common than CV deaths in our study group. Mortality in the never smokers (referent) was 6.2%. **Figure 27** shows the Cox regression analysis for total, CV and cancer mortality adjusted for age, sex, diabetes, hypertension and obesity.

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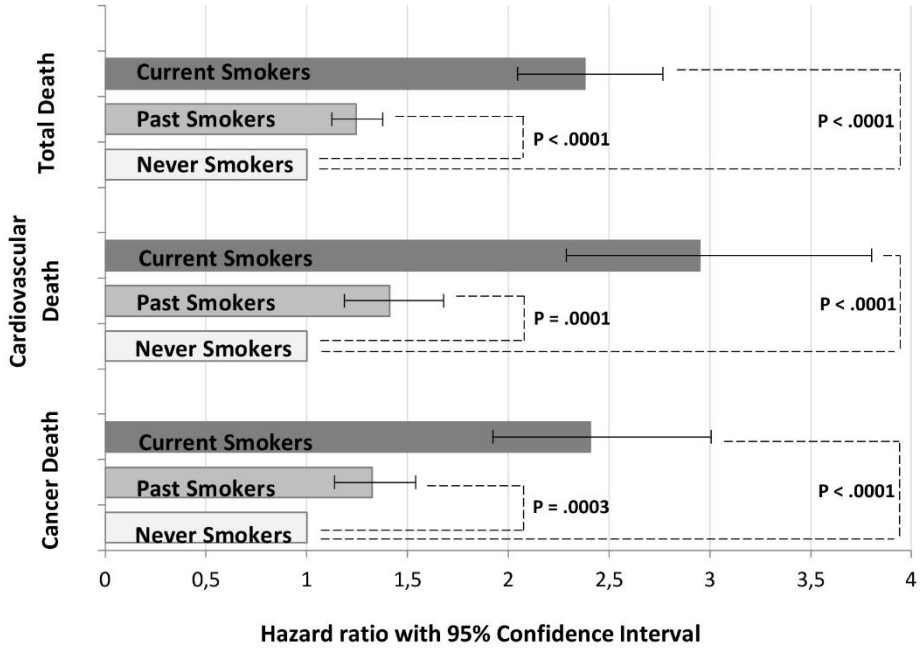

Figure 27. Hazard ratios with 95% confidence intervals for total, cardiovascular and cancer death adjusted for age, sex, diabetes, obesity and hypertension. Never smokers was the referent group. P values indicate significance of the hazard ratios compared to never smokers.

Never smokers formed the referent group for all analyses. Total, CV and cancer death rates were only slightly increased in past smokers versus never smokers but were much higher in current smokers. There was no overlap between CIs in any group. The hazard ratio was the highest for CV mortality in current smokers (2.95; 95% CI: 2.3 – 3.8).

We analyzed the effect of CRF on mortality in the smoking groups (**Figure 28**). Total mortality in never, past and current smokers was inversely related to CRF as shown on **Figure 28a**. Never smokers with normal CRF (FAC ≥ 100%) formed the referent group for the first part of the analysis; then we performed the comparisons within smoking groups using the normal CRF for each specific smoking group as the referent.

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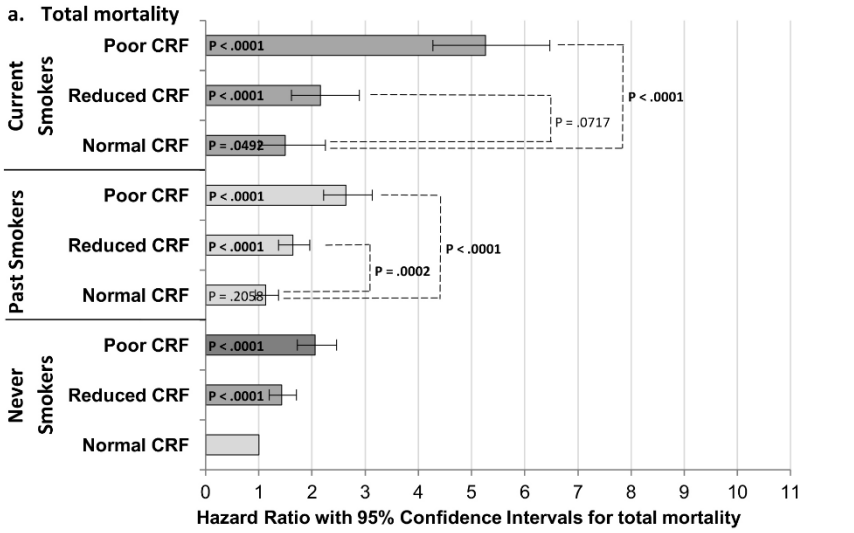

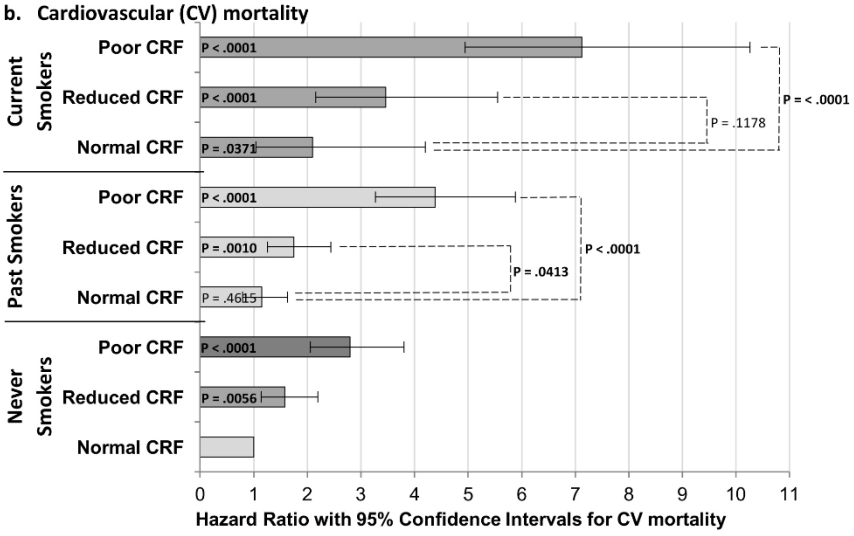

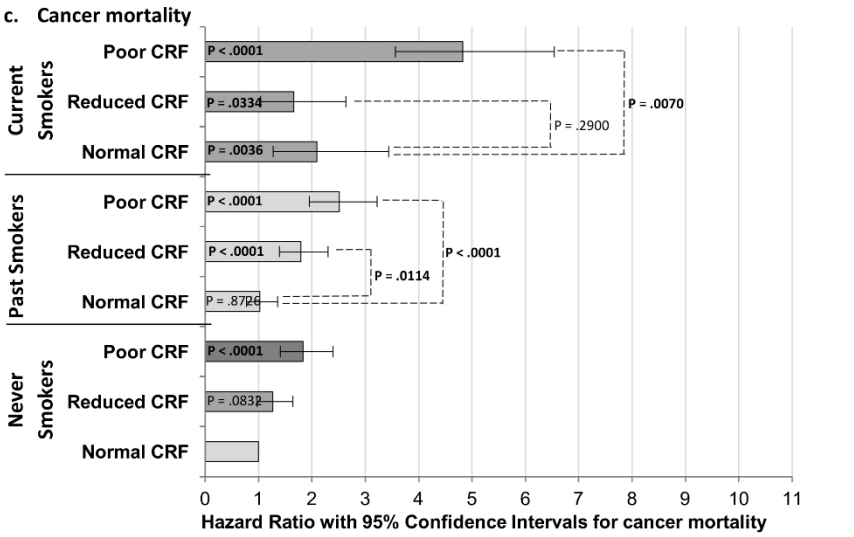

Figure 28. Hazard ratios with 95% confidence intervals for total mortality (3a), cardiovascular mortality (3b), and cancer mortality (3c) according to smoking status and level of cardiorespiratory fitness (CRF) adjusted for age, sex, diabetes, hypertension, and obesity. Never smokers with normal CRF was the referent group. P values in the bars indicate the significance of hazard ratios compared to referent group. Differences within the smoking groups indicated by dashed lines. P values indicate significance of the hazard ratios compared to normal CRF groups in never, past and current smokers.
CRF = cardiorespiratory fitness
Poor CRF = patients with FAC ≤ 80%
Reduced CRF = patients with 100 ≤ FAC < 80%
Normal CRF = patients with FAC > 100%

Compared to the normal CRF/never smokers, all groups except the normal CRF/past smokers showed increased risk of all mortality. The current smokers with poor CRF had the highest mortality (hazard ratio: 5.3 with 95% CI [4.3 – 6.5]). Patients with normal CRF had the lowest mortality in all smoking groups. According to the comparisons within the smoking groups patients with better CRF had lower mortality risk in past and current smokers as well. However, we did not find differences in the hazard ratios of reduced versus normal CRF (hazard ratio: 2.2 with 95% CI [1.6 – 2.9] versus. hazard ratio: 1.5 with 95% CI [1.0 – 2.3]) in current smokers. We did a secondary analysis using all never smokers as a referent group (not showing on the figure) and found that fit (CRF ≥ 100%) current smokers did not have increased mortality versus all never smokers (hazard ratio = 0.98; 99% CI: 0.67 - 1.50), and mortality of fit past smokers was actually lower versus all never smokers (hazard ratio = 0.80; 99% CI: 0.64 - 0.95). We analyzed CV and cancer mortality as well (**Figures 28b and 28c**). The pattern of cancer mortality was quite similar compared to total mortality, but the effect of CRF was more pronounced regarding the CV mortality between each group. The hazard ratio for total mortality in current smokers was 5.3 with 95% CI [4.3 – 6.5], while the hazard ratio for CV mortality in current smokers was 7.1 with 95% CI [4.9 – 10.3].

There were 200 (11.4%) patients (with 63 CV death and 116 cancer death) who died in the first three years of the follow-up. We excluded them from all mortality (total, CV, cancer and CRF level) to study if the pre-morbidity had any effect on our results. After their exclusion from the mortality analyses, our hazard ratios and P-values did not change significantly.

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5. Discussion

Our investigations have covered a broad approach to the clinical problem of establishing CV risk. The continuum of individuals studied ranges from young athletes and masters athletes with high levels of CV fitness, who would mostly be at the lowest possible risk level if not for their high intensity training and competitive performance, all the way to adults who are current smokers with very much reduced levels of CRF and at very high risk for total and CV mortality. A number of evaluative techniques – all involving some aspect of ECG – have been explored: the simple 12-lead resting ECG; long-term ECG recordings by Holter monitoring with special analysis of HRV; and exercise ECG. Although imaging now dominates the practice of cardiology, we show that there continues to be great power in the simple things – the resting ECG, the pattern of response of the HR, and the ability to perform aerobic exercise.

5.1. The Role of ECG in Athletic Screening

The screening of athletes with routine ECG requires substantial knowledge in the field of athletic adaptation. Many ECG findings that are considered abnormal in the general population can be normal in athletes as the result of extensive physical training. On the other hand, ECG abnormalities can be the first signs of CVDs that may lead to SCD in athletes. According to the latest guidelines of the European Society of Cardiology, athletic ECG changes can be divided into two groups: physiological, common, training related ECG findings and pathological, uncommon, training-unrelated ECG abnormalities. (96)

5.1.1. Physiological ECG Changes

As a result of the physiological adaptation, some training-related ECG signs appeared in almost every athlete in our study. Sinus bradycardia was observed in more than 50% of the athletes in accordance with earlier data, while only in about 10% of the controls. (158,159) As one of the most common training-related ECG finding, sinus bradycardia is most often attributed to high parasympathetic nerve activity. (22) However, several researchers question the essential role of vagal tone increase in the bradycardia of athletes. Reduced sympathetic tone or the decrease of intrinsic HR due to the remodeling of the sinoatrial node may also contribute to this phenomenon. (160)

As a result of enhanced autonomic regulation, marked sinus arrhythmia is also a common ECG finding in athletes. In some cases – mainly when it is associated with junctional beats following longer pauses – this functional AV-dissociation can be deceptive and may also imitate second or third degree AV block, therefore it has to be differentiated from severe AV-node diseases. (161) On the standard ECG recordings, no severe AV block was found in our population. Slowed AV conduction presenting as 1st degree AV block was observed in about 10% of the athletes. Athough, 1st degree AV block is considered to be training-related due to increased parasympathetic and decreased sympathetic tone in athletes (22), no difference was found between athletes and controls.

Incomplete right bundle branch block (IRBBB) was found to be present in about 30% of both groups. In contrast to earlier results, referring to this phenomenon as a result of RV adaptation to exercise, IRBBB was not more frequent in athletes compared to controls in our study. (162) If IRBBB is associated with other ECG abnormalities such as repolarization changes, clinical signs or symptoms, structural heart diseases such as

ostium secundum atrial septal defect must be excluded. We found this combination in one athlete without any structural heart abnormality. As IRBBB is a common feature in the children, its presence in athletes beyond 18 years of age may indicate retention of pediatric ECG features due to enhanced autonomic function and RV dilatation. Sinus arrhythmia, which was mentioned above as a common feature of the athletic ECG, is another pediatric ECG feature that continues into athletic adulthood.

5.1.2. Pathological ECG Abnormalities

In contrast to IRBBB, complete right bundle branch block (CRBBB) is categorized as a pathological ECG finding. Athletes with this ECG abnormality must undergo a thorough cardiac examination to exclude structural diseases, since ARVC or Brugada syndrome often manifest as CRBBB. (96) However, Kim et al. found that increasing QRS duration and CRBBB can be a result of more exercise training and RV enlargement in healthy athletes. (162) We found the presence of CRBBB in a single athlete, and subsequent detailed cardiac examination did not show any sign of structural heart disease. Another pathological ECG finding, left bundle brach block (LBBB) is uncommon in healthy individuals and it can be a strong and early ECG marker of ischemic or structural heart diseases. We found LBBB in only one athlete without any sign of ischemic or structural heart disease. Hemiblocks were also rare and there was no difference in the prevalence of left anterior and posterior hemiblock between athletes and controls. While left anterior hemiblock is more common and usually appears without evidence of structural heart disease, isolated left posterior hemiblock is very rare and if associated with RBBB, and it may reflect an increased risk of significant AV block. No bifascicular blocks were seen in our population.

In athletes, WPW-syndrome can lead to SCD due to the increased risk of atrial fibrillation and the occurance of FBI tachycardia. (163) Ventricular pre-excitation presented as delta-waves on the standard ECG was registered in two athletes. Frequency-dependent marked delta wave broadening was observed on their 24-hour Holter monitoring. Both of them underwent an electrophysiological testing and the accessory pathways were terminated with radiofrequency catheter ablation and they were permitted to continue sport.

Isolated voltage criteria for LVH were observed in more than 1/5 of the athletes, substantially more often than in the control group. LVH was considered pathological if

the voltage criterion for LVH was associated with at least one additional non-voltage criterion for example left atrial enlargement, left-axis deviation, ST-segment or T-wave abnormalities or pathological Q waves. Mainly because of the appearance of repolarization disorders, signs of pathological LVH were also diagnosed often in athletes and in controls. These changes can also point to structural heart diseases, which can lead to SCD. Primarily, pathological LVH has to be differentiated from HCM, which is the major cause of SCD in the United States (67). On a characteristic HCM ECG, T-wave inversion in two adjacent leads, deep septal Q-waves, signs of left atrial hypertrophy or arrhythmias (ventricular tachycardia, atrial fibrillation, supraventricular tachycardia) may be observed beside the QRS voltage criteria of LVH. (164) In the group of athletes with pathological hypertrophy ECG signs, no person was diagnosed with HCM with imaging methods. (165)

Referring to the repolarization abnormalities, training related ECG signs of early repolarization were the most frequent changes on the athlete's ECG in our study population. J-point elevation especially in precordial leads has been considered a benign, training related ECG finding. (166) In contrast, early repolarization appearing in inferior or lateral leads, particularly if associated with the widening of the terminal part of the QRS called notching or slurring may be associated with SCD. (107,108) In our study, early repolarization was mainly observed in precordial leads. QRS slurring or notching in inferolateral leads was found in 15 athletes without any other pathological changes during the detailed cardiac examination.

Although ST-segment elevation due to early repolarization is a common finding on the athletic ECG, ST-segment depression is rarely observed and is usually concomitant with T-wave inversion. (96) Besides the LVH, these ECG alterations are also recognized manifestations of HCM. Moreover, ST depression showed correlation with cardiac arrest in HCM patients. (31) ST depression can also be a sign of myocardial ischemia due to CAD mainly in athletes over 35 years of age, or may indicate anatomical abnormalities of the coronary arteries - especially in the young. (46) In the case of down-sloping ST segment elevation in the right precordial (V1-V3) leads, Brugada syndrome should also be considered. As compared to athletes, patients with the Brugada syndrome have lower Sokolow index, longer QRS duration, while the amplitude of maximum ST elevation is greater and does not present beyond right precordial leads and is rarely associated with

giant positive T-waves. (167) However, in athletes younger than 16 years of age and in Afro-Caribbean athletes the combination of early repolarization and inverted T-waves in precordial leads can be normal variants. (168) The differential diagnosis between Brugada–like pattern and athletic normal variant early repolarization is still challenging, but some new ECG criteria were established recently. (169,170) In our study, ST segment changes, mainly horizontal ST depression in inferolateral leads were also found more often in athletes compared to controls, whereas no underlying structural heart disease or chanellopathy could be diagnosed.

T-wave changes are considered to be common ECG abnormalities in athletes. According to the ESC recommendation T-wave inversion ≥ 2 mm in at least two adjacent leads is defined as pathological, however the significance of T-wave inversion < 2 mm is unclear and also suggested as a potentially pathological sign. (96) In our study T-wave inversion ≥ 1 mm was cathegorized as pathological also in accordance with the "Seattle Criteria". (158) In case of pathological T-wave inversion, HCM and Brugada syndrome should be considered as mentioned above. Moreover, ARVC should be excluded. ARVC, the major cause of SCD of athletes in Italy, is typically associated with T-wave inversion in V1-V3 leads with epsilon-waves, QRS prolongation or arrhythmias on the ECG. In our athlete group, T-wave inversion was the most common training unrelated ECG finding, observed in 15% of the athletes, compared to the 5% of controls. In most of our cases, T-wave inversion was observed in adjacent inferior or right precordial leads without any diagnosed cardiac diseases.

5.2. Autonomic Adaptation in Athletes

Physiological ECG changes and pathological ECG abnormalities are often observable during long-term ECG recording. However, Holter ECG has some other features to predict CV risk, such as HRV analyses. We showed that autonomic adaptation is a part of functional adaptation to exercise and it is concomitant to electrical adaptation. Intensive research of HRV as a marker of cardiac autonomic function was carried out in the past few decades. (40,41,53) Accordingly, several trials examined the influences of physical activity on HRV. The enhancing effect of training on HRV was observed in healthy participants as well as in CAD, heart failure, obesity, type-2 diabetes mellitus and following myocardial infarction. (120,121) In healthy participants, baseline autonomic status has been shown to be an important determinant of cardiac autonomic response to exercise. (122) Some previous studies also revealed an increase in HRV parameters in athletes versus healthy controls. (171,172) This was assumed to be a marker of chronic adaptation in athletes. As a characteristic of athletic conditioning, HRV analysis may be useful for following CV fitness development and determining optimal training intensity. (126) Some data have shown the correlation of HRV measures with ventilatory anaerobic threshold and lactate threshold, parameters also playing important role in the identification of appropriate physical training intensity. On the other hand, the decrease of HRV is used as a marker of overtraining and exhaustion. (114,119) Following high eccentric strength training, the decrease of specific high frequency domain HRV parameters beside the increase of low frequency HRV values was supposed to indicate autonomic imbalance towards sympathetic modulation predominance in healthy older men. (132) Moreover, those athletes who were trained taking into account the changes of their HRV parameters showed higher ventilatory threshold and better athletic achievements compared to the ones with fixed training plans that did not include adjustment for HRV. (115) However, the methodology of measuring and calculating HRV has not been standardized due to differring recording time and the variability of measured parameters. No systematic evaluation of the effects of different sports and training load on HRV has been previously made. Moreover, the low number of study participants, the short-term follow-up and the lack of athletic normal values did not allow the selection of athletes with pathologically decreased HRV.

5.2.1. Autonomic Adaptation by Sport Intensity

In our study, expressly higher time domain HRV parameters were calculated following long-term Holter monitoring in a composite group of 138 healthy athletes as compared to 100 controls. This phenomenon identifies the notable role of autonomic regulation in the adaptation of the athletic heart to the extreme load. In concordance with our results, a meta-analysis including short-term HRV measures of more than 300 athletes reported increased HRV values in athletes and presumed that the modality of sport and the unit of HRV measure could influence their results. (133)

We also studied the long term effect of performance on HRV time domain values for we could not find any other study comparing HRV values in elite and master athletes. After decades of high intesity physical training, the lower intensity activity did not affect HRV, as we did not find any difference between measurements of elite and master athletes. Our results proved that the enhancement of autonomic regulation due to more and higher intensity training was permanent. Therefore, master athletes had higher, not lower HRV versus the younger controls, the opposite of what might be expected based on the age difference alone. In connection with this, we did not find significant variation in HRV according to gender or age among the athletes. In accordance with our results, a 24-hour Holter monitoring study of active and sedentary master athletes also showed higher time domain parameters in active masters compared to sedentary counterparts. (172)

5.2.2. Autonomic Adaptation by Sport Modality

Our detailed analysis underlined that different sports activities affect the alterations of HRV, likely reflecting differing demands of training – such as endurance versus strength, continuous versus interval, ratio of training to competition. The highest HRV values were detected in canoe and kayak paddlers and bicyclists + triathlonists, while the lowest in runners. Concerning the lower outcomes in runners - mainly ultramarathon runners, - the results are independent of their higher age because age-corrected values were used. A single study also evaluated the long-term HRV measures in different sports disciplines in low number of athletes and controls. While they found higher RMSSD, pNN50 and frequency domain HRV values in both groups of athletes compared to the controls, SDNN values elevated only in endurance athletes compared to controls. (173) In contrast, in our analyses we did not find any difference in SDNN values between different sports.

5.2.3. Clinical Perspectives

As we only have normal values for short-term HRV in both children and adults, and there are no data on standard HRV values in athletes, we also determined the normal athletic HRV time domain values suitable for referencing HRV results in individual athletes. Decreased HRV may draw attention to an underlying CV abnormality, therefore using our normal values, HRV analysis can be powerful components of risk stratification of athletes in the future. We believe our results together with further research will facilitate the adequate use of HRV measurements in selecting athletes for competition, monitoring and optimizing training, and spotting over-training as well as in potentially identifying athletes at risk for malignant arrhythmias in the future.

5.2.4. Limitations

Long-term Holter recording especially in top athletes undergoing daily trainings did not allow us to prohibit physical exercise; therefore, part of the studied athlete group trained 1–2 hour during monitoring. Transient increase of sympathetic tone and the decrease of parasympathetic tone during physical activity as well as the opposite changes during recovery could affect our results although the above described changes of HRV could also be observed in athletes not training during Holter monitoring. Another potential limitation of the study is that athletes were not studied at the same phase of training - some were in competitive phase, others in base training phase, or even in off-season, and we did not have complete data on the amount and the intensity of actual training for every athlete. Moreover, we did not have many master athletes in their mid-50s or older or who have been intensely training for more than 30 years. Thus, we cannot exclude the possibility that the decrease of HRV may eventually start to occur at a certain age. A final limitation is that this is a cross-sectional study, so what we call effect of age is not based on using the participant as his or her own control over time but is based on the analysis of athletes of different ages.

5.3. Exercise Heart Rate Responses in Non-Athletes

HR is the basis of ECG, Holter ECG and exercise testing. On an exercise test, functional and HR parameters seem to be more important than evaluation of ST segments. Our exercise ECG study was designed to evaluate the gender differences in HR responses and to determine if a separate equation for predicting peak HR for women is justified. After first eliminating patients with CVD or taking drugs affecting HR, then eliminating those with comorbidities affecting peak HR, we show that most HR responses to exercise are significantly different in men versus women. Women have higher resting HR at all ages. HR reserve is higher in men at all ages, principally due to lower resting HR. HR recovery, however, is statistically significantly different between men and women only in the age group 50 - 59. Peak HR is significantly lower in younger women compared to men, but declines more slowly with age such that peak HR at ages 70-79 and 80-89 is not significantly different between men and women. While the HR response of men in our cohort was almost identical to the traditional 220 – age formula, a lower intercept (210 bpm) and slope (0.79 bpm/year) are required to predict peak HR in women. All exercise HR parameters have an inverse linear relationship to age in both men and women.

Risk factors such as diabetes, smoking, obesity, and poor exercise performance are associated with lower peak HR, perhaps secondary to less than maximal physiologic versus perceived effort. Respiratory distress, for example, may cause a smoker to stop exercising before cardiac output has reached its limit. We eliminated all these risk factors to get a pure cohort and determined that a separate formula for peak HR in women seems appropriate, because the traditional formula of 220 – age overestimates peak HR in younger women (age 40 – 50) and underestimates in elderly women (age 50 – 90).

5.3.1. Peak Heart Rate Prediction

HR responses to exercise have been studied for many years in various populations. All studies report a strong inverse relationship between peak HR and age. The traditional equation to predict peak HR (220 – age) for both men and women was established by Fox et al in a small cohort of 220 subjects, mostly men under age 55. (134) Subsequently, a meta-analysis on 18,712 subjects performed by Tanaka showed a different regression equation to predict peak HR, but the regression lines were not different for men and women (men: peak HR = 209 – 0.73 x age; women: peak HR = 208 – 0.77 x age). (139)

In Tanaka's meta-analysis, only healthy (defined by non-ischemic ECG response), non-medicated, non-smoking subjects were involved, although we have no exact information about exclusions for CVD, diabetes and hypertension. Tanaka also performed a complementary laboratory study in a healthy population using non-medicated and non-smoking adults without CAD to verify the maximal level of effort by VO_2 testing (using a respiratory exchange ratio ≥ 1.15 as indicative of maximal effort). The regression lines derived (men: peak HR = [210 – 0.72 x age] vs. women: peak HR = [207 – 0.65 x age]) were very similar to the meta-analysis findings, again without significant differences by sex. In Tanaka's two studies, men more so than the women show HR responses that differ from our data. Though we generally take the traditional formula for peak HR in men for granted, our confirmation that 220 – age is an appropriate formula for predicted peak HR in men is not an insignificant finding in the present study.

We have previously published findings from our laboratory (137) on exercise HR in a study that focused on exercise BP response in 7863 men and 2406 women without CVD or hypertension. That cohort was tested in an earlier time frame (1988-1992), and we did not restrict the cohort according to diabetes, smoking or poor test performance. Regression equations for peak HR were 213 – 0.90 x age for men and 203 – 0.76 x age for women with the lower intercepts observed versus the present study likely due to the less restricted nature of the earlier cohort.

An analysis of exercise tests in the St. James Women Take Heart Project performed by Gulati et al (135) proposed a women's formula for age-predicted peak HR = 206 – 0.88 x age. This was a volunteer cohort of 5,437 asymptomatic women but no men were tested identically for comparison. Women included were age 35 years or older, had no active CVD, and were able to walk on a treadmill at a moderate pace, but diabetics and smokers were not excluded.

5.3.2. Clinical Importance

The present study is not only the largest clinical cohort analyzed to compare peak HR versus age in men and women; but also presents important normative data for other HR parameters including resting HR, HR reserve, and HR recovery. We also show the impact of selected risk factors in attenuating the peak exercise HR, potentially allowing us to reconcile differences in peak HR response among the various published studies.

Peak HR is one of the most commonly used parameters in clinical CV medicine, so correct determination is important. On one hand, peak HR can be used to determine the adequacy of exercise testing with a target of at least 85% of predicted maximal HR. (141) Using the wrong target HR for women may theoretically result in unnecessary repeat testing, though we project that < 1% of tests would be reclassified as adequate versus inadequate with most of those being in older women where traditional versus new predicted HR differences become progressively larger. From another perspective, poor HR response to exercise signals an adverse prognosis, so again an inappropriate target may result in incorrect interpretation in selected patients. (12,141,174-176) Estimated peak HR is also used to prescribe exercise intensity for various types of patients when no exercise test was performed. (177) Our study both confirms the use of the traditional 220 – age formula for men but also provides further evidence that a different formula should be utilized for women.

5.3.3. Limitations

This is a cross-sectional analysis with single tests from different individuals. A longitudinal study with regularly repeated tests on a fixed population of healthy individuals would be more appropriate for determining the true physiological effect of aging on exercise HR, but such a study would be much more difficult to conduct.

These exercise tests were conducted in a clinical environment in which patients were instructed to exercise to subjective fatigue. Patients were not specifically "pushed" to continue exercise until a definite plateau in HR was observed, nor did patients undergo repeat testing to be certain that a higher exercise HR could not be achieved on a second or third try. Gas exchange was not measured during exercise to confirm effort by respiratory exchange ratio.

We had a limited number of patients older than 80 years in our clinical cohort, and survival bias may have affected the HR responses of these older patients. Older individuals are also more likely to have orthopedic complaints that could represent a potential limitation of exercise HR. The differences that we have noted in peak HR between men and women are not nearly as high as the variation in peak HR at any given age (SD ~ 11-15 bpm depending on the age group). Thus, slightly adjusting the equation for predicting peak HR will not greatly improve the estimate of peak exercise HR for an

individual female patient. Rather, the male-female differences in HR response to exercise shown here may lead us to an additional understanding of sex differences in aging.

Younger patients were excluded from this study, because we felt there was a significant referral bias. Syncope, chronic fatigue, congenital cardiac disorders, tachyarrhythmias, morbid obesity, and screening for sports participation are among the common referral diagnoses in younger subjects. Thus we felt that their HR would significantly deviate from the regression line versus age derived in older patients. An analysis of the patients aged 20 – 39 in our database confirmed these suspicions. Both peak HR and its decline with age were less vigorous in this younger population (men: peak HR = 193 – 0.40 x age; women: peak HR = 196 – 0.61 x age).

This study was not designed to specifically determine why the HR responses are different by sex. It is unlikely that sex-differences in attitudes toward physical activity play a role, and the large number of women being tested obviates biases that test personnel might have against pushing women to high levels of effort. We might speculate that sex hormones are involved. High testosterone levels promote increased muscle mass in men at young ages, allowing then to push to higher exercise intensities and higher peak HRs during exercise compared to women, but declining testosterone levels gradually attenuate exercise intensity and HR in older men. Muscle mass and exercise performance may follow a less rapid decline in relatively testosterone-poor women. Further research of a more physiologic nature is obviously indicated.

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5.4. Risk prediction on Exercise Test

We extended our research on special patient populations as smokers. We investigate the effect of CRF on comorbidities and mortality in never, past and current smokers. Past smokers had a significantly greater prevalence of obesity, hypertension, and diabetes compared to never smokers, while current smokers did not show an increased prevalence and risk of these comorbidities compared to never smokers but had much higher rates of poor CRF. Total, CV and cancer mortality was only slightly increased in past smokers versus never smokers; but mortality was much higher in current versus past smokers despite lower rates of weight-associated comorbidities. We assume that weight gain after quitting smoking was largely responsible for the increased rates of diabetes and hypertension seen in the past smokers. Higher mortality in current versus past smokers was obviously not related to obesity, diabetes, and hypertension, but low CRF was likely a factor.

5.4.1. Effect of Cardiorespiratory Fitness on Mortality

Better CRF showed protective effect in all smoking groups. Prior to this investigation, there has been no study which validated the effect of CRF in smoking on a large low risk population.

Besides our study there are only two papers which investigate the association between exercise, smoking habit and mortality. (148,178) O`Donovan et al included almost 100,000 patients; the amount of exercise was assessed by a questionnaire. According to their results a greater amount of exercise was associated with decreased total, CV and cancer mortality, while greater amount of smoking resulted in increased risks for mortality. In both current and past smokers, exercise accounted for an approximate 30% mortality reduction. Moore et al pooled data from six prospective cohort studies and found generally the same outcomes regarding total mortality. In our study, current smokers with poor CRF had 5.3 times higher all-cause mortality risk, 7.1 times CV and 4.8 times higher cancer mortality risk, while in past smokers these risks were 2.6, 4.4 and 2.5. These findings can likely be explained by the comprehensive protective effect of exercise.

Some studies have proposed a beneficial effect of CRF on mortality in smokers. According to survey data from Finland, in active smokers aged 40-60, the mortality risk was higher among those who were physically inactive or moderately active. (179) In our study we compared the mortality according to CRF within the smoking groups as well. Better CRF had a strong protective effect in all smoking groups. The mortality of fit past smokers was not significantly different compared to fit never smokers, which shows how powerful is the effect of quitting smoking in mortality.

It is well known that smoking is the leading cause of cancer death; however in smokers, the prognostic impact of exercise on cancer mortality has not been previously established. There is one large study published by Moore SC. et al which found that increasing levels of leisure-time physical activity were associated with lower risk of 13 of the 26 investigated cancer types in different populations including obese individuals and/or smokers. (180) There are some smaller studies which also investigated the effect of exercise and smoking on specific cancer types. Their data suggest that exercise and smoking cessation may prevent cancer progression and reduce cancer death. (181-183)

5.4.2. Clinical importance

The strengths of our study include a large consecutive cohort with complete mortality follow-up over a long time period. We also can stratify mortality according to CV and even cancer death. Exercise test data were robust and complete, and important data on comorbidities and pharmacotherapies were available. Our study reflected the limited racial diversity seen in Minnesota, so our results may not be applicable to more diverse racial or ethnic groups. Overall mortality was low, reflecting the status of Minnesota as a state with low total and CV mortality. We might speculate that the protective effect of CRF might be even more important in a higher risk population.

5.4.3. Limitations

Our study has some limitations. First of all, it was a referral population. Because these patients were predominately Caucasian and from the state with the lowest CVD rates in the US, the study cohort likely was at lower CV risk than the general population. Exclusion of baseline CVD from this cohort further lowered risk. So, in a general

population, the differences by smoking status might be expected to be more dramatic than what we documented here.

Another potential limitation is that past smoking history was not quantified in terms of pack years, and the time since smoking cessation was not considered. Given the time course of smoking rates in the US, we think it is likely that many of the past smokers were not recent quitters. The significantly higher rates of obesity and obesity-related comorbidities support a longer period of non-smoking. Recent quitting and limited smoking history introduce negative rather than positive bias to the study findings by minimizing differences among the 3 smoking groups.

The possibility of secondary (passive) smoking was also not included in this study.

The stress tests were conducted in clinical circumstances, and patients were instructed to exercise to subjective fatigue. Gas exchange was not measured to confirm the level of metabolic effort by respiratory exchange ratio. We are using CRF at a single time point. The exercise test may thus reflect recent, rather than lifetime physical activity patterns, though it is clear from survey data that low levels of physical activity in the US have been persistent over many years. It is unlikely that a significant portion of the poor CRF in any of the groups is predominately due to recent changes in behavior.

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6. Conclusions

According to our results, the athletes' ECG data showed a significant physiological electrical and structural adaptation but in some cases potentially pathological abnormalities may be revealed. In our study of a composite sample of asymptomatic Hungarian athletes, we have found no underlying structural heart disease either in individuals with ECG abnormalities. However, with a thorough evaluation of ECG, we could recognize athletes as being at a potentially higher risk, therefore we suggest regular CV follow-up. Our study is a representative sample of Hungarian athletic ECG changes, therefore we believe that an exact definition and widespread knowledge of athletic ECG is essential in early recognition of high risk athletes.

Athletic adaptation can also be investigated with long-term ECG recording. On a routine Holter ECG recording we can get important information about the status of the autonomic nervous system. In athletes, long-term time-domain parameters of HRV were proved to be higher compared to controls. This indicates that autonomic adaptation is a part of athletic adaptation reflecting a dominant parasympathetic tone. Moreover, these parameters vary according to sports modality referring to the role of autonomic system in the sport-specific adaptation of the heart. According to our findings, autonomic adaptation of athletes is permanent, because the elevated HRV values remain unchanged in masters athletes. As we have determined normal athletic values, therefore using our lower cut off values may also detect athletes at high CV risk based on decreased autonomic adaptation.

ECG recording during exercise testing is another important method of risk assessment. In our studies we focused on the prognostic parameters from the exercise test, and we have also identified the clinical factors which modify these prognostic parameters. HR responses to exercise are age and sex related. Women have higher resting HR rate, lower HR reserve and lower peak HR compared to men. Observing these sex differences brought up the idea that predicted equation in women may have to be different. In our large cohort, after eliminating factors negatively affecting peak HR, the equation predicting peak HR in men was nearly identical to the traditional formula but peak HR in women had a lower intercept and decreased more slowly with age. A separate formula for peak HR in women seems to be appropriate.

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Exercise HR responses are different in many pathological conditions. In our research we have focused on the effects of smoking. Although past smokers showed higher rates of comorbidities (obesity, diabetes, hypertension, and low CRF), their mortality was only mildly increased compared to never smokers. Current smoking, however, carried a high mortality risk despite lack on an increase in CV comorbidites versus never smokers. These data suggest that quitting smoking is beneficial despite increased comorbidities. Exercise may potentially mitigate the risk of both comorbidities and death in those who quit smoking. Overall, we can conclude that exercise testing is an important diagnostic method and it has potential important prognostic value to detect patients at high risk.

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SUMMARY

Electrocardiography (ECG) is an essential tool for diagnosis and management of athletes and patients with cardiovascular (CV) diseases. Although imaging now dominates the practice of cardiology, with detailed evaluation of different ECG techniques, we can increase the diagnostic power of this simple, low cost method.

The purpose of our studies was to emphasize the importance of ECG in athletic screening, to show the additional diagnostic potential of long-term ECG recording in athletes, to present the predictive value of non-ECG prognostic factors on the exercise test in an adult referral population and to define the role of functional aerobic capacity (FAC) and heart rate (HR) responses in predicting risk according to smoking status.

We highlight the prevalence of physiological ECG changes and potentially pathological ECG abnormalities in a representative sample of Hungarian athletes versus controls. Although we have not found any underlying structural heart diseases in athletes with training-unrelated ECG changes, their regular follow-up is necessary, therefore widespread knowledge of ECG is essential in early recognition of high risk athletes. Athletic adaptation can also be investigated with Holter ECG recording, which provides important information about autonomic regulation with heart rate variability (HRV). Time-domain parameters of HRV are higher in athletes compared to controls, and vary according to sports modality and intensity. Our lower cut off values may detect athletes at high CV risk based on decreased autonomic adaptation.

In our exercise testing studies we focus on prognostic parameters and their affecting factors on a large cohort of non-athletes. HR responses to exercise are age and sex related, with women having higher resting HR rate, lower HR reserve and lower peak HR compared to men. After eliminating factors negatively affecting peak HR, the equation predicting peak HR in men is nearly identical to the traditional formula, but in women this has a lower intercept and it decreases more slowly with age. Exercise HR responses are different in many pathological conditions such as smoking. Although past smokers show higher rates of comorbidities, their mortality is only mildly increased compared to never smokers. Our data suggest that quitting smoking is beneficial despite increased comorbidities. Exercise may mitigate the risk after quitting smoking. Exercise testing is an important diagnostic method, but it has potential important prognostic value to detect patients at high risk.

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ÖSSZEFOGLALÁS

Az elektrocardiographia nélkülözhetetlen a sportolók és szívbetegek kivizsgálásában és irányításában. Bár napjainkban a képalkotó vizsgálatok dominálnak a kardiológiai gyakorlatban, a különböző EKG technikák részletes elemzésével növelhetjük ezen egyszerű és olcsó vizsgálat diagnosztikus potenciálját.

Vizsgálataink célja az EKG jelentőségének hangsúlyozása a sportolói szűrésben, a hosszú távú EKG monitorozás jelentőségének bemutatása sportolóknál, a prognosztikus paraméterek prediktív értékének vizsgálata terheléses vizsgálaton átesett betegeknél, valamint a terhelési kapacitás és terheléses szívfrekvencia válaszok prediktív szerepének meghatározása dohányzási státusz szerint.

Vizsgáltuk a fiziológiás EKG eltérések és a potenciálisan patológiás EKG elváltozások előfordulási gyakoriságát magyar sportolók reprezentatív mintáján kontrollcsoporthoz képest. Bár a sportterheléstől független EKG eltérések hátterében strukturális szívbetegség nem igazolódott, rendszeres utánkövetésük szükséges, ezért a sportolói EKG eltérések széleskörű ismerete nélkülözhetetlen a magas rizikójú sportolók korai felismerésében. A sportadaptáció vizsgálható Holter EKG-val is, mely szívfrekvencia variabilitás vizsgálatokkal (HRV) értékes információkkal szolgálhat az autonóm szabályozás állapotáról. A HRV idő paraméterei magasabbak sportolókban kontrollokhoz képest; sporttípus és intenzitás szerint változnak. Az általunk meghatározott alsó cut off értékek segítségével felismerhetőek a csökkent autonóm adaptációval rendelkező magasabb kockázatú sportolók.

Terheléses vizsgálatainkban a prognosztikus paraméterekre koncentrálva vizsgáltuk a befolyásoló faktorok szerepét nem-sportolóknál. A terheléses szívfrekvencia válaszok nem és életkor függők, a nők nyugalmi frekvenciája magasabb, frekvencia rezervje és maximális frekvenciája alacsonyabb. A befolyásoló faktorok eltávolítását követően az életkornak megfelelő maximális frekvencia számítása férfiaknál nagyjából megegyezik a hagyományos képlettel, nőknél azonban alacsonyabb és kevésbé csökken az életkorral. A terheléses frekvencia válaszok kórosak pathológiás állapotokban, például dohányzásnál. Bár a volt dohányosoknál a társbetegségek gyakoribbak, mortalitásuk kevésbé emelkedett a nem dohányzókéhoz képest. A sport csökkentheti a dohányzás okozta emelkedett rizikót. A terheléses vizsgálat egy fontos diagnosztikus módszer, valamint prognosztikus értéke miatt alkalmas a magas rizikójú betegeket kiszűrésére.

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   IF: 0.814

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