Sudden cardiac arrest in relation to exercise

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“You can’t accomplish anything without the possibility of failure.”

Lazarus Lake

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ABSTRACT

Background: In predisposed individuals with a known or unknown cardiovascular disease, the risk of a sudden cardiac arrest is increased during and immediately after exercise. The most common postmortem diagnosis of exercise-related cardiac death in the young is Sudden Arrhythmic Death Syndrome (SADS).
Aims: The aims of this thesis were to describe incidence, demographics, circumstances of resuscitation and prognosis among victims of exercise-related Out-of-Hospital Cardiac Arrest (OHCA). Furthermore, we aimed to describe the phenotype of SADS in the young.
Methods: This thesis is based on observational studies with the use of national quality registers. The Swedish Registry of Cardiopulmonary Resuscitation (SRCR) was used to identify cases of OHCA and to describe circumstances of resuscitation. The registry of the Swedish National Board of Forensic Medicine, the Swedish Cause of Death Registry, the Swedish National Patient Registry, the Swedish Prescribed Drug Registry were used to identify cases of SADS and to describe their phenotype. Each case of SADS was assigned five population-based controls from Statistics Sweden.
Results: The incidence rate of exercise-related OHCA in the general population in Sweden was 1.2 per 100.000 person years. The 30-day survival rate was significantly higher for exercise-related OHCA compared to non-exercise related. Survival rates were higher at sports arenas compared to outside arenas. Exercise-related OHCA was rare

among females, however they had a much worse prognosis compared with males. Victims aged 0-35 years had the highest survival rates. Of all SCDs among 1-35 years-old, SADS accounted for 22%. A higher proportion av SADS victims experienced previous cardiac symptoms and were in contact with healthcare providers prior to death, as compared to controls.

Conclusion: Victims of exercise-related OHCA have significantly higher survival rates compared to non-exercise-related OHCA, partly due to favorable circumstances of occurrence. Female victims of exercise-related OHCA have low survival rates, which indicates a need for increased knowledge and awareness of exercise-related SCA in females. SADS accounted for a lower proportion of SCDs in the young, compared to previous studies. Prior symptoms and contact with healthcare providers offer possibilities to identify individuals at risk of SADS.

Keywords: sudden cardiac arrest, sudden cardiac death, OHCA, exercise-related OHCA, resuscitation, exercise-related cardiac arrest, sports cardiology, sudden arrhythmic death syndrome, CPR, AED, SRCR

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Hos individer med underliggande känd eller okänd hjärtsjukdom, kan kraftig fysisk ansträngning öka risken att drabbas av ett plötsligt hjärtstopp. Den vanligaste diagnosen som ställs postmortem vid idrottsrelaterad plötslig hjärtdöd bland unga är så kallad SADS (Sudden Arrhythmic Death Syndrome). I dessa fall har man vid obduktion inte funnit någon säker förklaring till döden, varpå man misstänker primär hjärtrytmrubbning som dödsorsak.

Syfte: Syftet med avhandlingen var att beskriva förekomst av, prognos samt faktorer som påverkar överlevnad för hjärtstopp, vilka sker i anslutning till fysisk aktivitet. Vidare ville vi beskriva karakteristika hos unga individer som gått bort i SADS för att kartlägga möjliga riskfaktorer i denna grupp.

Metod: Svenska Hjärtlungräddningsregistret användes för att identifiera fall och beskriva omständigheterna för hjärtstopp som skett i anslutning till fysisk aktivitet. Rättsmedicinalverket och dödsorsaksregistret användes för att identifiera fall av SADS. Ur Nationella patientdataregistret och Läkemedelsregistret insamlades information om tidigare sjukhistoria respektive förskrivna läkemedel. Vidare granskades patientjournaler, obduktionsrapporter samt journaler från mönstringar. För varje fall av SADS kopplades fem kontroller.

Resultat och slutsatser: Förekomsten av hjärtstopp i anslutning till fysisk aktivitet i Sverige var 1.2 fall per 100.000 personer och år. Överlevnaden var betydligt högre för hjärtstopp som skett i anslutning till fysisk aktivitet jämfört med övriga hjärtstopp utanför sjukhus och utanför hemmet, delvis till följd av högre bevittnandegrad och kortare tid till HLR. Kvinnor hade emellertid betydligt sämre prognos jämfört med män, vilket signalerar ett behov av ökad kunskap och medvetenhet om hjärtstopp vid fysisk aktivitet hos kvinnor. SADS stod för 22% av alla fall av plötslig hjärtdöd hos unga. En högre andel av personerna som avled i SADS hade föregående symtom och hade sökt sjukvård jämfört med kontroller, vilket medför en möjlighet för oss att identifiera personer under risk att drabbas av SADS.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Frisk Torell M, Strömsöe A, Zagerholm E, Herlitz J, Claesson A, Svensson L, Börjesson, M. Higher survival rates in exercise-related out-of-hospital cardiac arrest compared to non-exercise related – a study from the Swedish Register of Cardiopulmonary Resuscitation. *European Journal of Preventive Cardiology*. 2017; 24: 1673-1679.

II. Frisk Torell M, Strömsöe A, Herlitz J, Claesson A, Svensson L, Börjesson, M. Outcome of exercise-related out-of-hospital cardiac arrest is dependent on location: Sports arenas vs outside of arenas. *PLOS ONE*. 2019; 14. e0211723. 10.1371/journal.pone.0211723.

III. Frisk Torell M, Strömsöe A, Herlitz J, Claesson A, Rawshani A, Börjesson, M. Better outcomes from exercise-related out-of-hospital cardiac arrest in males and in the young: findings from the Swedish Registry of Cardiopulmonary Resuscitation. *British Journal of Sports Medicine*. 2022;56: 1026-1031.

IV. Frisk Torell M, Svennblad B, Wisten A, Börjesson E, Bergfeldt L, Stattin E-L, Börjesson M. Sudden arrhythmic death syndrome (SADS) causing cardiac arrest in the young – what can we learn from prior medical and family history, ECG and preceding symptoms? *In manuscript*

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ABBREVIATIONS

ACM	Arrhythmogenic cardiomyopathy
AED	Automated external defibrillator
AHA	American heart association
AMI	Acute myocardial infarction
ARVC	Arrhythmogenic right ventricle cardiomyopathy
BrS	Brugada syndrome
CAA	Coronary artery anomaly
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CI	Confidence interval
CPR	Cardiopulmonary resuscitation
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CVD	Cardiovascular disease
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
EMS	Emergency medical services
ERS	Early repolarization syndrome
ESC	European society of cardiology
HCM	Hypertrophic cardiomyopathy

LISA	Swedish longitudinal integrated database for health insurance and labor market studies
LQTS	Long QT syndrome
MAP	Medical action plan
MRI	Magnetic resonance imaging
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PED	Primary electrical disease
ROSC	Return of spontaneous circulation
SADS	Sudden arrhythmic death syndrome
SAEDREG	Swedish AED registry
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death
SRCR	Swedish registry of cardiopulmonary resuscitation
SUDDY	Sudden cardiac death in the young cohort
SVT	Supraventricular tachycardia
VT	Ventricular tachycardia
VF	Ventricular fibrillation
WPW	Wolf Parkinson White

PREFACE

June 12th, 2021. Denmark is playing against Finland in the European Football Championships at Parken Arena in Copenhagen. 13,790 excited supporters at the arena, and more than a billion TV spectators are watching the game.

Forty-three minutes into the game, the Danish player Christian Eriksen suddenly and unexpectedly collapses after receiving the ball from a throw-in. The famous Eriksen have experienced a sudden cardiac arrest and lies unresponsive on the ground. Eriksen's teammate Simon Kjaer instantly realizes the severity of the situation, rushes to him and puts him on the side to secure his airway. Shortly after, Denmark's team physician along with a crew of medical personnel assemble around Eriksen and starts CPR. A defibrillator is brought to the scene and after delivering a shock, Eriksen is successfully resuscitated.

The Christian Eriksen event was traumatic, not just for his teammates and family but for all the spectators. Furthermore, it raised a lot of concerns and questions.

Why is it that seemingly healthy individuals suffer sudden cardiac arrest and die during exercise? Exercise, that supposedly is so important for maintaining health. How can exercise be dangerous and for whom? How common is this? Could we prevent exercise-related sudden cardiac arrest from happening and what can we do to be prepared and handle these situations more effectively to prevent death?

INTRODUCTION

SUDDEN CARDIAC ARREST AND SUDDEN CARDIAC DEATH IN RELATION TO EXERCISE

SUDDEN CARDIAC ARREST

Sudden cardiac arrest (SCA) is defined as a sudden cessation of normal cardiac activity, followed by hemodynamic collapse. (1) If no attempts at resuscitation are made, this condition progresses to sudden death.

IS EXERCISE DANGEROUS?

There is strong scientific evidence to support the beneficial effects of regular physical activity. (2-5) However, in a predisposed individual, with known or subclinical cardiac disease, physical activity of high intensity could act as a trigger for a SCA. (6-12) This increased risk is particularly evident in individuals with habitual sedentary lifestyles, who suddenly embark in strenuous physical activity. (6, 13) Thus, here lies the paradox, thereby physical activity is associated with health promoting effects in a vast majority but could be the trigger for a malignant arrhythmia in a minority with underlying structural or electrical cardiac disease.

INCIDENCE

When comparing incidence rates of exercise-related SCA or sudden cardiac death (SCD) in different studies and populations, there is quite a variety. (7, 14) Different methods used to identify victims, as well as incohesive definitions of both cases and their denominator are contributing factors. (15, 16) A generally accepted definition of exercise-related SCA/SCD is a SCA or SCD occurring during or within 1h after cessation of physical activity. (17-19) In studies of exercise-related SCA in the general population, incidence rates range from 0.5-2 per 100.000 person-years. (17, 19, 20) Although exercise-related SCA/SCD is rare in younger age groups (<35 years), competitive young athletes have an up to 4.5-fold increase in incidence rate compared to the recreational athletes of the same age. (19) During the last decades, from 1990 to 2010, the incidence of exercise-related SCD in the young in Sweden luckily has decreased by almost 50%. (21)

The frequency of underlying cardiac conditions predisposing for SCA/SCD varies between different populations and correlates with type of sport, thereby affecting incidence rates of exercise-related SCA/SCD. (22, 23) For example, incidence rates are much higher among Black athletes compared to Caucasians, and especially male Black basketball players have been identified as a high-risk population. (7, 24) In addition, incidence rates are much dependent of sex, with males having up to a 10-fold increased risk of SCA compared to females. (17, 25)

Much focus has been on the youngest athletes, however with increasing age the prognosis is worse compared to young and adolescent athletes. (19)

UNDERLYING CONDITIONS AND MECHANISMS

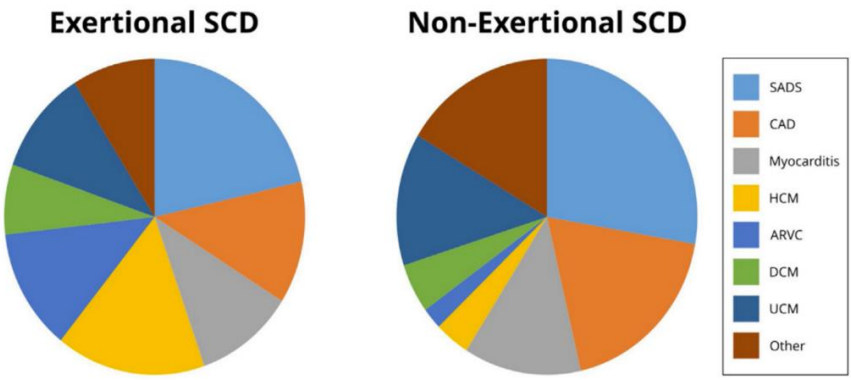


Figure 1. Cause of death related to SCD in men aged 10-35 years in Sweden 2000-2010. SADS: sudden arrhythmic death syndrome, CAD: coronary artery disease, HCM: hypertrophic cardiomyopathy, ARVC: arrhythmogenic right ventricular cardiomyopathy, DCM: dilated cardiomyopathy. Reproduced from Wisten et al. Resuscitation Volume 144. November 2019, with permission from Elsevier.

Depending on age and ethnicity, the underlying conditions causing exercise-related SCA/SCD varies in frequency. (26-28) In younger age groups, especially <25 years, SCA/SCD is mainly caused by inherited cardiovascular conditions. (11, 18, 29, 30) Figure 1 describes the results from a previous Swedish autopsy-based study of

exercise-related SCD in 0–35-year-olds, in which the most common diagnosis was Sudden Arrhythmic Death Syndrome (SADS). (21) This is consistent with findings from several previous studies. (7, 26, 28, 31) With increasing age, the proportion of coronary artery disease (CAD*)* as the underlying etiology of exercise-related SCA increases steadily (Figure 2). (27, 29, 32)

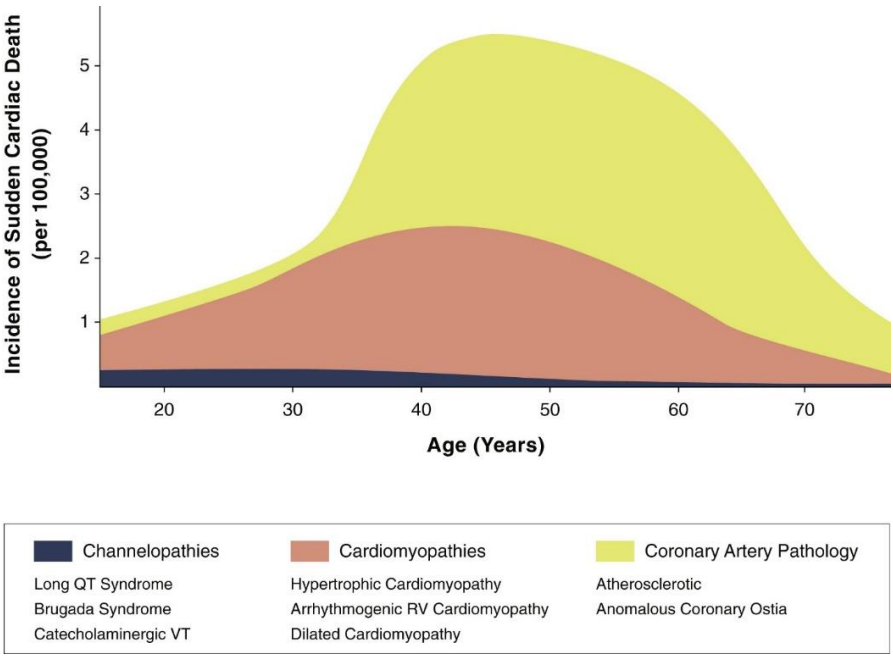


Figure 2. Age-dependent Changes in Incidence and Etiology of Sudden Cardiac Death in athletes. Reproduced from La Gerche et al. JACC: Cardiovascular Imaging Volume 6. September 2013, with permission from Elsevier.

VENTRICULAR FIBRILLATION

Ventricular fibrillation (VF) is a common endpoint in many underlying conditions with potential to cause exercise-related SCA. For VF to evolve, mechanisms include the emergence of a reentry phenomenon. Reentry refers to a self-generating electrical circuit, which sustains the wave of depolarization through the myocardium**.** The exact

mechanism of VF has been debated. Mainly, two different mechanisms have been proposed. First, the "mother-rotor hypothesis", in which one or a few reentrant circuits (rotors) act as a source of the fibrillatory activity. Second, is the "multiple wavelet mechanism", which implies that multiple disorganized wavelets of electric activity are responsible for the VF. More recent studies support a combination of both these theories. (33, 34) Whether a single rotor or multiple wavelets, they tend to occur in the barrier between healthy and somehow damaged myocardium, which is seen in structural cardiac disease. (33) Ventricular arrhythmias can also occur because of a disruption of the heart's electrical stability on a cellular level, which is the case in primary electrical and genetic ion-channel abnormalities.

CORONARY ARTERY DISEASE

Myocardial infarction (MI) is one of the most common predisposing factors for VF in adults. (35) The absolute incidence of exercise associated MI in a Swedish material is 0.75 per 100.000 person-years. (36) However, MI is not a necessity to induce VF in subjects with CAD, since ischemia itself can alter electrical conduction and predispose to arrhythmias even without manifest infarction. (37) In addition, the development of scar tissue and fibrosis in the myocardium following episodes of ischemia, can act as a substrate for malignant arrhythmias. (38)

CONGENITAL CARDIAC CONDITIONS

CORONARY ARTERY ANOMALY

Coronary Artery Anomalies (CAAs) are congenital conditions characterized by either abnormal origin or course of any of the three main coronary arteries. As a result, coronary artery blood flow could be compromised, especially during exercise, causing myocardial ischemia, ventricular arrhythmias and SCA/SCD. (11, 27, 39) The prevalence of CAA was previously estimated to be $\leq$ 1%, mainly based on results from invasive coronary angiography and autopsies. (40, 41) With increasing use of Coronary Computed Tomography Angiography (CTTA), more recent studies have revealed prevalence rates of 2-7%. (42-44)

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic CardioMyopathy (HCM) is a hereditary condition with an autosomal dominant pattern of inheritance, but the disease can also occur as result of de novo mutations. The prevalence of HCM has been estimated to be 0.2%. (45-47) The disease is characterized by abnormal thickening of the myocardium, primarily in the

left ventricle. As a result of hypertrophy, obstruction of blood flow can occur, leading to ischemia and infarction. Within the thickened myocardium, areas of fibrosis and ischemia pose as substrates for ventricular arrhythmias. (48-50)

ARRHYTHMOGENIC CARDIOMYOPATHY

Arrhythmogenic Right Ventricle Cardiomyopathy (ARVC) is mainly caused by mutations responsible for coding desmosomal proteins, leading to the replacement of normal myocardium by fibrotic and fatty tissue. The disease could be inherited both as autosomal dominant and as recessive. The penetrance of the predisposing genetic mutations varies, and environmental factors likely contribute to differences in phenotype expression. Initially, the disease was thought to exclusively affect the right ventricle. However, many patients have been found to have biventricular involvement. (51, 52) Therefore, the new term Arrhythmogenic cardiomyopathy (ACM) have been introduced to describe myocardial abnormalities including fat infiltration and fibrosis, affecting both ventricles. (53) Exercise has been proposed to accelerate the process of ACM/ARVC, since among gene carriers, the ones with high exercise load and endurance athletes were more likely to fulfill the diagnostic criteria for ARVC. (54) Exercise leads to increased right ventricular volume, likely stressing the vulnerable desmosomal junctions, affected by genetic mutations in ACM. (55) In subjects with manifest disease, both competitive and recreational sport activities have been shown to correlate with a higher risk of arrhythmias. (54, 56)

DILATED CARDIOMYOPATHY

Dilated CardioMyopathy (DCM) is a condition with global hypokinesia of the ventricles, which are dilated and often fibrotic. Abnormal loading conditions and CAD should be excluded as causatives before diagnosis. Typically, it is a progressive disease leading to worsening in ventricular function with heart failure and ventricular arrhythmias as consequences. (57) Several predisposing genetic mutations have been identified, but many cases of DCM occur idiopathically. In addition, extrinsic factors such as chemotherapy or excess use of alcohol have been shown to trigger the evolvement of DCM, especially in genetically predisposed individuals. (58)

PRIMARY ELECTRICAL DISEASE

Primary Electrical Disease (PED), also known as inherited channelopathies, are rare conditions with underlying genetic alterations in genes responsible for ion channels located in myocardial cell membranes. Normally, the electrical activation through the

myocardium is strictly balanced by ion currents over cell membranes and intracellular calcium regulation. By affecting these mechanisms, PEDs pose a risk of disrupted electrical stability, with induction of ventricular arrhythmias. Brugada Syndrome (BrS), Long QT Syndrome (LQTS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and Early Repolarization Syndrome (ERS) are all examples of PED. (59, 60)

In PED, the susceptibility to arrhythmic triggers varies between different syndromes. Vigorous exercise with abrupt increase in sympathetic tone is known to trigger ventricular arrhythmias in both LQTS and CPVT. (61-64) In subjects with underlying BrS as well as ERS, arrhythmic inducing factors are those resulting in bradycardia, such as betablockers and vagal stimulation. Infectious disease, especially when accompanied with fever, could also lower the threshold for arrhythmias in PED. (62, 65, 66)

PREEXCITATION

Ventricular preexcitation refers to a premature activation of the ventricles in relation to the expected activation through the AV-node. A characteristic finding, although not always present, is a short PQ-interval and a slurred upstroke in the beginning of the QRS-complex (delta wave) seen on electrocardiogram (ECG). This ECG pattern indicates the presence of an accessory electrical pathway between the atria and ventricles, in addition to the normal His-Purkinje system. The accessory pathway can conduct electrical impulses in either antegrade or retrograde direction, and in some cases in both directions. If conducted in antegrade direction, the typical preexcitation pattern on ECG will appear. However, if the accessory pathway only conducts impulses in retrograde direction, the QRS complex will have a normal morphology during sinus rhythm. While the AV-node can limit or “slow-down” the conduction of impulses to the ventricles, the accessory pathway usually does not have the same electrical properties, but instead conducts impulses rapidly. Therefore, a rapid re-entry tachycardia can occur by using the AV-node and the accessory pathway as a re-entry circuit. Wolf-Parkinson and White first described patients with preexcitation and the associated tachycardia, and thereby named it Wolf-Parkinson White Syndrome (WPW). The prevalence of ventricular preexcitation varies between 0.1-0.3% in the general population. (67, 68) If a patient with preexcitation develops atrial fibrillation, there is a risk of antegrade conduction over the accessory pathway, resulting in VF.

Not all patients with a preexcitation pattern on ECG will develop tachyarrhythmias. (69) However, asymptomatic preexcitation does not guarantee a low risk of future arrhythmias and SCA. (70, 71) Thereby, there is a clinical dilemma in how to manage patients with preexcitation without symptoms.

MYOCARDITIS

Myocarditis is an inflammatory condition, mostly caused by viral infections. Direct damage to the myocardium occurs by pathogens infiltrating the myocardium but also trough activation of the immune system, causing acute edema. Furthermore, cardiac remodeling and scarring could occur, with a potential to develop into DCM. (72) Myocarditis poses a risk for arrhythmias both in the acute phase and more long-term, if leaving a fibrotic scar. In autopsy based studies on SCD in athletes, myocarditis has been found to account for 8-10% of all deaths. (21, 73) It is recommended that athletes with active myocarditis are withheld from competitive sports for 3-6 months and are evaluated by a new echocardiography or a cardiac Magnetic Resonance Imaging (MRI), an exercise test and Holter-monitoring before returning to sports. (72, 74, 75)

COMMOTIO CORDIS

Commotio cordis is caused by blunt trauma to the chest wall, for example by a baseball or hockey puck, resulting in VF, without causing structural damage to the heart. The mechanical force delivered to the chest wall seems to cause a stretch in myocardial cell membranes, thereby affecting ion channels. To trigger a VF, the contact typically must occur during the ventricular repolarization phase of the heart, i.e. during the T-wave upstroke. In addition, the stroke requires a specific amount of energy and force to be able to produce a VF. (76)

SUDDEN ARRHYTHMIC DEATH SYNDROME

Accounting for the highest proportion of SCDs in the young (<35 years) in Europe, a diagnosis of SADS suggests a primary arrhythmic event as cause of death. (21, 26, 77, 78) These are unexplained cases of SCD with no structural abnormality found on autopsy and with a negative toxicology screen. (79-82) The frequency of SADS as underlying etiology of SCD in the young, varies comparing different study populations, with proportions ranging from 10-20% of SCDs in young athletes, and up to 40% of all SCDs in the young. (26, 78, 83) The addition of genetic analyses has

been shown to decrease the proportion of SADS, by identification of inheritable cardiac diseases, such as PED. (84, 85)

EXTERNAL FACTORS

Different external factors could increase the risk of arrhythmias in a predisposed or vulnerable individual. Numerous medications are known to potentially affect ion currents across myocyte membranes, resulting in prolongation of the QT interval. (86) Furthermore, there are illicit drugs associated with a higher risk of VF and SCD. For example, cocaine use is known to cause intense vasoconstriction resulting in obstructed coronary blood flow/spasm and following ischemia with a potential to induce VF. (87, 88)

During exercise, various aggravating factors could potentially lower the threshold for arrhythmias and SCA. A sudden release of catecholamines during exercise, followed by a decrease in vagal tone, can result in increased susceptibility to arrhythmias. (89) Intense physical activity also affects platelet activation and could induce a hypercoagulable state, possibly contributing to a transient increase in risk of cardiovascular events during exercise. (90) Mechanical forces and shear stress on arterial walls have also been proposed to increase the risk of plaque ruptures with concomitant SCA.(91)

In addition, there are factors related to type of activity/sport and the environment it is performed in. For example, participants in long distance running races are at increased risk of metabolic complications, hyponatremia, hyperthermia and dehydration. (92) These are all conditions with potential to lower the arrhythmic threshold.

PREVENTION OF EXERCISE-RELATED SCA

SCREENING

Elite athletes are recommended to be regularly evaluated in a cardiac pre-participation screening, to identify individuals at risk of SCA. (93, 94) In Sweden it is recommended that screening involves all elite athletes from age 16. (95) However, adherence to recommended screening is far from 100%. (96)

The rationale behind pre-participation screening is the benefits reported after the introduction of a screening program among elite cyclists in the Veneto region in Italy, were the incidence of SCD (mainly HCM related) dropped markedly. (97) The screening protocol typically includes a family history, physical examination and a 12-lead ECG. (98) To increase the specificity of screening, there are guidelines for the interpretation of ECGs in athletes. (99).

Not all cardiac conditions can be detected by screening. CAD is particularly challenging, since it accounts for a major proportion of SCA/SCD in athletes aged 25 years and older (32) and, in case of stable CAD, is not easily detected by a standard screening procedure including only a 12-lead resting ECG. (100, 101)

In addition, screening of athletes aged > 35 years is not as well established as for younger athletes, and even though the majority of SCA/SCDs in absolute numbers occur during recreational sports, elite athletes are the focus of cardiac screening. (19)

Regarding screening of elderly subjects, the European Society of Cardiology (ESC) recommends a physical examination, including an exercise-test in sedentary persons aged >65 years before they embark in physical activity of moderate to high intensity. (53) How to implement this recommendation and whether it is motivated in a Swedish population is still unknown.

RESUSCITATION

Not all cardiac conditions can be detected prior to SCA/SCD. Even with widespread screening of athletes, we cannot prevent all exercise-related SCA from happening. As in Cristian Eriksen's case, an immediate response and effective resuscitation is crucial for survival.

THE HISTORY OF RESUSCITATION

"Suscitare": latin meaning "to awaken" or "to arouse".

The modern resuscitation technique includes three elements (components): ventilation, chest compressions and defibrillation. Each of these elements have evolved through a process of trial and error over centuries.

Already in biblical scripts, there is mentioning of bringing people back to life. Exodus for example, contains a story of a midwife bringing newborns back to life by "blowing" into their mouths. Thereafter, continuous trials of different techniques to bring people back from the dead have been documented. Warming of bodies, body positioning, blowing smoke into them. The use of internal chest compressions was first described by prof Maritz Shift, Florence 1874. (102) By the end of the 19th century, several reports of successful resuscitation by external chest compressions emerged from around the world. Dr Friedrich Maas describes the resuscitation of a 9-year-old boy suffering from cardiac arrest after anesthesia with chloroform.

" I now had to consider the patient dead". Nevertheless, I went to direct compression of the heart region, and in my excitement, I worked very fast and vigorously. The pupils quickly constricted and when I continued at great speed, they were soon smaller and during pauses, the slow gasping respiration started up again." (103)

THE EVOLVEMENT OF PREHOSPITAL CARE

During the Napoleon wars, a field surgeon named Dominique Jean Larrey developed a new way of transporting injured soldiers from the battlefield. By introducing "*ambulances volantes*" (flying ambulances), he revolutionized prehospital care. The flying ambulances consisted of light, horse driven carriages with either two or four wheels, depending on whether they were to be used mainly on flat ground or in mountain terrain. The injured were then transported to heavier vehicles, which ultimately took them to a hospital. Larrey further established a system of triage of the wounded, depending on the severity of their injuries and need for urgent treatment, regardless of military grade nor nationality. (104)

Larrey was truly ahead of his time and it was not until 1967, Pantridge *et al*. presented the benefits of using a mobile intensive care unit in treatment of myocardial infarctions, which was the starting point of the prehospital emergency care we have today. (105) In analogy, the mobile emergency care in Sweden was introduced by Stig Holmberg in the 1970s and together with Bertil Wennerblom, they showed that the use of a mobile coronary care unit was able to reduce mortality in both myocardial infarction and cardiac arrest. (106)

THE CHAIN OF SURVIVAL

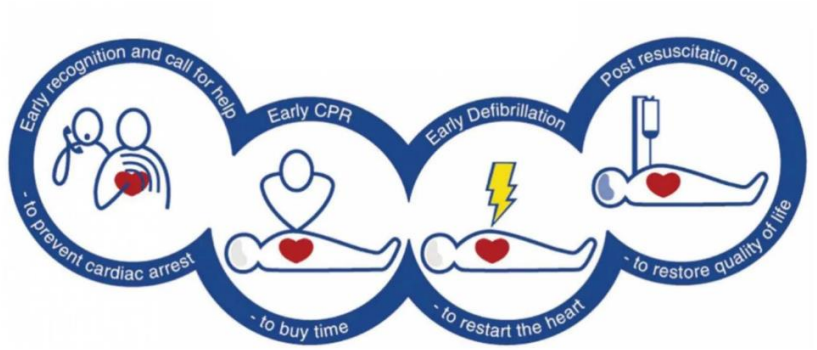


Figure 3. The Chain of survival. Reproduced from Perkins et al. Resuscitation Vol 95. October 2015, with permission from Elsevier.

The advanced resuscitation technique used today, was initially declared by the American Heart Association in 1991 and is well illustrated by the chain of survival, which highlights key factors for survival in case of SCA. (107) The chain of survival, illustrated in Figure 3, includes a series of interventions starting with (1) early recognition and call to emergency services; (2) prompt CPR; (3) early defibrillation; (4) early advanced care, including (5) post-resuscitation care; followed by (6) rehabilitation. (108)

The greatest impact on survival is observed in the immediate response to a SCA, i.e. the first three links in the chain of survival. (109) In out-of-hospital cardiac arrest (OHCA), the first recorded rhythm is a strong predictor for survival. Ventricular arrhythmias (pulseless ventricular tachycardia and ventricular fibrillation) are shockable rhythms, which can be converted to normal heart rhythm by defibrillation. In contrast, non-shockable rhythms (pulseless electrical activity and asystole) do not respond to an electrical shock delivered by a defibrillator and are associated with worse prognosis. (110, 111)

TRENDS

In Sweden, the chance of surviving a SCA outside of hospital has increased since 1990. (112, 113) Similar trends have been observed globally. (114-116) Increased

rates of bystander CPR and the increased availability of public AEDs are important contributing factors to the higher survival rates seen today. (112, 113, 117, 118) Nevertheless, the survival rates of OHCAs in Sweden remained relatively constant around 10%, between 2011 to 2022. (113)

Possible explanations for this stagnation in survival rates of OHCAs, are a declined proportion of shockable rhythm, as first recorded rhythm after collapse, during the last decades, which in turn correlates with increased EMS response time. (119, 120) In fact, the median delay time to EMS arrival in Sweden increased from 6 to 11 minutes from 1990 to 2020. (113) In correlation, the proportion of cardiac arrests defibrillated by EMS decreased during 2000-2010, even though the frequency of public AED use increased during the same period. (121) Another contributing factor explaining the decrease in shockable rhythm as the first recorded rhythm in OHCA, is the decrease in presumed cardiac disease as the underlying cause of OHCA during the last decades. (113) However, the latest annual report from the Swedish Registry of Cardiopulmonary Resuscitation (SRCR) showed some encouraging results by presenting the highest survival rates for OHCA ever recorded in Sweden:12,4%. (122)

ARENA SAFETY

To be able to handle acute medical emergencies including SCA at sports arenas, trained medical personnel and proper equipment including AEDs is of essence. (1, 123) Increased availability of public AEDs have been associated with higher survival rates of SCA in different settings, including sports facilities. (121, 124, 125) A study from the Swedish AED Registry (SAEDREG), showed that the number of registered public AEDs doubled from 2013 to 2016, with most of public AEDs being located in workplaces or offices (45%), followed by shops (7%). Only 6% of the registered public AEDs were located at sports facilities. (126) Little is known of at what extent public AEDs are used in exercise-related SCA in Sweden.

At US High schools equipped with AEDs, the integration of AEDs as part of an emergency action plan, has been associated with higher SCA survival rates. (127) To reach the goal of early CPR and early defibrillation at sports arenas, it is recommended that each arena has a written medical action plan (MAP). (123)

RATIONALITY FOR THIS THESIS

Previous studies on exercise-related cardiac arrest have been somewhat incohesive in terms of definitions, denominators, and study methods. Focus tends to be the youngest athletes, understandably since a SCA in a young athlete is a devastating, traumatic event. However, the majority of exercise-related SCA/SCDs doesn't occur among young elite athletes, but during amateur- or recreational sports with increased risk with increasing age. Therefore, we wanted to describe exercise-related SCA in the general population, of all ages.

Even though SCA and SCD are reported to be infrequently occurring, especially in the young, the lack of standardized definitions and registration of these cases poses a risk of wrongly estimating true incidences. Thereby, our ability to calculate risks and the cost-effectiveness of cardiac screening as well as emergency action planning will be affected.

Sweden's national quality registries offer a unique opportunity to study exercise-related SCA/SCD in the general population and SCD due to SADS. We can present reliable incidence rates of exercise-related SCA occurring outside of hospital, in all age groups as well as SADS in the young and describe circumstances of occurrence and possible risk factors.

Furthermore, we can highlight factors of major importance for survival in the event of SCA and identify factors that could be improved in the management and prevention of SCA/SCD. By careful characterization of previous victims of SCA and SCD, we can increase our knowledge, which is a prerequisite to prevent and increase survival of SCA.

AIMS

The overall aim of this thesis was to increase our knowledge in SCA occurring in relation to exercise. We wanted to present accurate incidence rates of exercise-related OHCA in the general population. We also wanted to compare the prognosis and circumstances of exercise-related OHCA compared to non-exercise-related OHCA and to identify variables associated with better chance of survival.

Because the likelihood of bystander CPR and AED availability is higher at sports arenas compared to outside of sports arenas, we wanted to compare survival rates and circumstances between these two settings.

Among exercise-related OHCA, we aimed to investigate possible differences between males and females as well as different age groups in terms of prognosis and circumstances of resuscitation.

Since SADS is the most common diagnosis of exercise related SCD in the young in Sweden, we wanted to study this population further. Specifically, we wanted to describe their prior medical and family history, previous symptoms and ECG findings to identify possible risk factors for SADS in the young.

PATIENTS AND METHODS

DEFINITIONS

For this thesis, different terms have been used to describe the study cohorts, depending on the setting. In the first three papers, only cases of SCA occurring outside-of-hospital were included and therefore, the main term used in these papers is exercise-related OHCA. In the fourth paper, the term SCD is used, since the study population includes both out-of-hospital SCD and in-hospital SCD**.**

SUDDEN CARDIAC ARREST

In the SRCR, a SCA occurring outside of hospital is included if resuscitation ie CPR and/or defibrillation has been attempted by anyone. If the EMS crew on arrival find definite signs of death, such as rigor mortis, corpse stains or injuries incompatible of life, the case is excluded from the SRCR, even if a bystander has initiated resuscitation attempts.

SUDDEN CARDIAC DEATH

Sudden cardiac death was defined as an unexpected death from cardiac causes occurring within 1h after onset of symptoms if witnessed. In unwitnessed cases, it was defined as an unexpected death in a person observed to be well within 24h prior to being found deceased. (78, 128) Deaths due to homicide, suicide, intoxication, trauma, and drowning were excluded. Cases with a primarily non-cardiac cause of death were also excluded.

EXERCISE-RELATED SUDDEN CARDIAC ARREST/SUDDEN CARDIAC DEATH

A sudden cardiac arrest occurring during or up to 1h after cessation of physical activity was defined as an exercise-related sudden cardiac arrest. (17, 18)

SPORTS ARENA

A sports arena was defined as a public location utilized for the purpose of physical activity, both competitive and recreational.

SUDDEN ARRHYTHMIC DEATH SYNDROME

SADS was defined as a SCD with no distinct structural abnormality (macroscopically or histopathological) found on autopsy and with negative toxicology screen. (80, 82, 129, 130)

STUDY POPULATIONS

PAPER I

The study population consisted of all cases of OHCA outside of home registered in the Swedish Registry of Cardiopulmonary Resuscitation (SRCR) between 1st January 2011 and 31st December 2015 reported in three of Sweden's 21 counties: Västra Götaland, Halland and Dalarna. In total, 1825 cases of OHCA were included. Information concerning factors at resuscitation, survival and assumed etiology of the arrest was obtained from SRCR. Additional information regarding location and activity at time of the arrest, specifically whether the arrest occurred in relation to exercise or not, was extracted from manual search in EMS medical records and in-hospital medical records.

PAPER II

All cases of OHCA outside of home between 1st January 2011 to 31st December 2014 reported in ten counties in Sweden were identified from the SRCR. In total, 3714 cases of OHCA occurred during the study period and out of those, 268 cases were classified as exercise related OHCAs and included as the study population.

PAPER III

For this study, the identification of study subjects occurred from two different time periods. The first study period reached between 1st January 2011 to 31st December 2014 and included all exercise-related OHCAs outside of home in nineteen counties of Sweden. The second study period reached between 1st February 2016 to 31st December 2018 and for this period, cases of exercise-OHCA outside of home in all 21 counties of Sweden were identified from the SRCR. For the first time period, the variable "exercise-related" was determined by manual search in EMS medical records and in-hospital medical records. For the second time period, a question whether the OHCA occurred in relation to physical activity or exercise, had been

included in the SRCR as a mandatory variable at registration. In total, 636 cases of exercise-related OHCA were identified and included in the study.

PAPER IV

Cases of SADS occurring between 2000 and 2010 among 1–35-year-olds in Sweden, were extracted from the SUDden cardiac Death in the Young cohort (SUDDY). In total, 149 cases of SADS were included together with five-population based controls. Data from medical records, ECGs, death certificates, clinical - and forensic autopsies was analyzed. Register data from several national registers was used to describe demographics, prior health care contacts and ICD specific diagnoses for cases and controls.

DATA SOURCES

THE SWEDISH REGISTRY OF CARDIOPULMONARY RESUSCITATION

The SRCR was founded in 1990. Over the years the completeness of the registry has increased and since 2010 nearly 100% of all out-of-hospital cardiac arrests where resuscitation has been attempted are covered. All Emergency Medical Services (EMS) in Sweden report to the registry. Inclusion criteria are cases of OHCA with performed CPR and/or defibrillation by either lay persons or paramedics. A health care professional, either from the EMS or another prehospital unit, registers information for each case of OHCA, immediately or close after the event. Additional data from in-hospital medical records is reported by a local CPR coordinator (mostly a senior nurse) after either discharge from hospital or death. A complete registry form includes information on location and probable etiology of the arrest, the resuscitation procedure such as delay times, witness degree, and immediate outcome. In a previous validation study of the SRCR from 2013, approximately 75% of OHCAs, where resuscitation was attempted, were reported to the registry prospectively by EMS crews and the remaining were reported retrospectively.(131) How the proportions of reporting are distributed today/the last ten years, has not been studied.

THE NATIONAL BOARD OF FORENSIC MEDICINE

In Sweden, all individuals undergoing a forensic autopsy is registered in the National Board of Forensic Medicine. A standardized protocol is used for each autopsy, according to consensus guidelines. (132) The registry contains death diagnoses, coded according to the International Classification of Diseases (ICD), circumstances of death and a medical background. Included in the forensic report are also eventual police reports and results from toxicology screen and histopathology analyses.

GOVERNMENTAL REGISTERS HELD AT THE NATIONAL BOARD OF HEALTH AND WELFARE

THE CAUSE OF DEATH REGISTRY

Death certificates for all deaths occurring in Sweden are registered in the Cause of Death Registry (CDR) since 1952.(133) A death certificate includes main diagnosis and secondary diagnosis relevant to the death and is issued by the physician responsible for the deceased. In case of additional previous diagnoses or conditions relevant to the death, they are also included in the death certificate. If a forensic or clinical autopsy is performed, results from the autopsy will also be registered in the CDR.

THE NATIONAL PATIENT REGISTRY

The National Patient Registry (NPR) was established in 1964 and since 1987 it has a complete nation-wide coverage of inpatient care. In 2001, data from public hospital-based outpatient care was added to the registry. However primary care is not covered by the registry. (134) A previous validation of the NPR concluded that 85-95% of the diagnoses in the inpatient registry were valid. (135) The NPR contains information on all hospital admissions (inpatient as well as outpatient visits) and includes International Classification of Diseases (ICD) codes for each visit.

THE PRESCRIBED DRUG REGISTRY

The Prescribed Drug Registry (PDR) was launched in 2005 and includes data on all prescribed and dispensed drugs in Sweden. Within the PDR, drugs are sorted into groups according to the Anatomical Therapeutic Chemical classification system. (136)

THE MULTIGENERATION REGISTRY

Since 1932,the MultiGeneration Registry (MGR) comprises information on all Swedish residents, including relationships with both biological and adoptive parents.(137)

THE REGISTER OF THE TOTAL POPULATION AND POPULATION CHANGES

The Register of the Total Population and Population Changes (TPR) was established in 1967 and is maintained by the government agency Statistics Sweden. The TPR includes information on name, age, sex, birthplace, place of residence, citizenship, migration, civil status and family relationship. (138)

THE LONGITUDINAL INTEGRATED DATABASE FOR HEALTH INSURANCE AND LABOR MARKET STUDIES

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA, Swedish: Longitudinell Integrationsdatabas för Sjukförsäkring och Arbetsmarknadsstudier) was established in 1990. LISA covers data on socioeconomic variables such as educational degree, income, sick leave, disability pension and civil status for individuals aged $\geq$ 16 years since 1990 and from the age of 15 since 2010. (139)

STUDY DESIGN

A retrospective register-based study design was utilized in all studies included in this thesis. Paper I-III are based on data from the Swedish Registry of Cardiopulmonary Resuscitation. Paper IV is based on the linking of several national registries, described above.

STATISTICAL METHODS

PAPER I

In this study descriptive statistics were used, and variables presented as numbers, percentages, mean and median. To evaluate proportions for binary variables, non-parametric test: Fishers Exact Test was used. For continuous variables, Wilcoxons two-sample test was used. A p-value of <0.05 was regarded as significant. Logistic

regression was used to calculate the age adjusted odds ratio (OR) and accompanying 95% confidence intervals (CI) for survival at 30 days.

PAPER II

A comparative analysis was made between cases of exercise-related OHCA occurring at sports arenas versus cases of exercise-related OHCA occurring outside of arenas. Descriptive statistics were used. Variables are presented as numbers, percentages, mean and median. Non-parametric test: Fishers Exact Test, was used to compare proportions for binary variables and Wilcoxons two-sample test was used in the comparison of continuous variables. A p-value of <0.05 was considered significant. Two sided tests were applied. Logistic regression was used to estimate differences in age adjusted survival rates and was described as ORs with 95% CI.

PAPER III

Descriptive statistics were used, and variables presented as numbers, percentages, mean and median. In the comparison of proportions, non-parametric test: Fishers Exact Test was used for binary variables. Wilcoxons two-sample test was used in the comparison of ordered and continuous variables. A p-value of <0.05 was considered significant. Two sided tests were applied. For the covariates age, gender, bystander witness, time from collapse to start of CPR, initial rhythm and time to EMS arrival, a multivariate regression model was used. ORs as well as their 95% CI were calculated.

PAPER IV

To present numbers and percentages, descriptive statistics were used. Age distribution is presented as mean and median. In comparison of cases and controls, conditional logistic regression was used. A Likelihood Ratio test comparing models with and without the variable as well as the Wald test of the beta coefficient are presented. A p-value of ≤ 0.05 was considered statistically significant. ORs and accompanying 95% CI were calculated.

ETHICS

PAPERS I-II

Ethical permission was authorized by the ethical committee in Stockholm (2015), with Dnr 2015/1122-31/5.

PAPER III

Ethical permission was authorized by the ethical committee in Stockholm (2019), with Dnr 2019-03514 with completion 2021-00018.

PAPER IV

Ethical permission was authorized by the ethical committee at Umeå University (2012), Dnr 2012-161-31M, with completion Dnr 2013-317-32M, Dnr 2014-156-32M, Dnr 2015-376-32M, Dnr 2016-105-32M, Dnr 2016-428-32M, and Uppsala University (2017). Dnr 2017/430, 2017/431.

RESULTS

PAPER I

In total, 1825 OHCAs outside of home were registered in SRCR during the study period. Of these 1825 OHCAs, 137 (7.5%) occurred in relation to exercise. The incidence rate of exercise-related OHCA was 1.2 per 100.000 person-years. A male predominance was seen in both exercise-related (n=132, 96.4%) and non-exercise-related (n=1230, 72.9%) OHCAs. Mean age ± standard deviation (SD) in the exercise-related group was 56.4 ± 15.3 years compared to 67.2 ± 16.5 years in the non-exercise-related group. The 30-day survival rate was significantly higher among exercise-related OHCAs compared to non-exercise-related: 54.3% and 19.4% respectively ($p<0.0001$). The age-adjusted odds ratio for 30-day survival in exercise-related compared to non-exercise-related OHCA, was 4.60 (95% CI 3.17-6.69, $p< 0.0001$).

Regarding circumstances of resuscitation, exercise-related OHCAs were more likely bystander witnessed (89.4% vs 78.6%, $p=0.002$), received bystander CPR more frequently (80.3% vs 61.0%, $p<0.0001$) and were more often connected to a public AED (20.4% vs 4.6%, $p<0.0001$), compared to non-exercise-related OHCAs. Victims in the exercise-related group more frequently had a shockable rhythm compared to victims of non-exercise-related OHCA (72.6% vs 46.6%, $p<0.001$). Median delay times from collapse to call for emergency services (2.0min), from collapse to CPR (1.0min) and to defibrillation (11.0 vs 12min), did not differ significantly between the groups. Patient characteristics and circumstances of resuscitation are presented in Table 1.

In both groups, presumed cardiac etiology was the most common diagnosis: 85(70.2%) of the exercise-related OHCAs and 990 (64.2%) of the non-exercise related, p=0,20. Cycling (n=29, 21%) was the most common sport activity associated with exercise-related OHCA, followed by gym workout/group training (n=16, 12%), golf (n=14, 10%) and running (n=11, 8%).

Table 1. Patient characteristics and circumstances of resuscitation in relation to exercise

	Exercise-related	Non-exercise-related	p-value
	n=137	n= 1688	
Age (mean±SD), (2,81) *	56.4 ± 15.3	67.2 ± 16.5	<0.0001
Females, (0,0)	5 (3.6 %)	458(27.1%)	<0.0001
Bystander witnessed, (5,65)	118(89.4%)	1276(78.6%)	0.002
CPR before EMS-arrival (5,41)	106(80.3%)	1004(61.0%)	<0.0001
AED connected before EMS-arrival (5,86)	27(20.4%)	73(4.6%)	<0.0001
AED connected by firs-responders (3,58)**	18(13.4%)	212(13.0)	0.89
Shockable rhythm (13,96)	90(72.6%)	741(46.6%)	<0.0001
Presumed cardiac etiology (16,146)	85(70.2%)	990(64.2)	0.20
Delay times (medium, min)			
Collapse-call (82,680)	2.0	2.0	0.40
Collapse-CPR (103,1120)	1.0	1.0	0.14
Collapse-defibrillation (67,556)	11.0	12.0	0.40
Survival to 30 days (6,55)	70(54.3%)	315(19.4%)	<0.0001

AED, automated external defibrillation; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; SD, standard deviation.
*Missing data
** Firefighters or police

PAPER II

During the study period, between 2011 to 2014 in 10 counties in Sweden, 3714 cases of OHCA outside of home were reported to SRCR. In total, 268 (7%) occurred in relation to exercise. In six cases, information about the place of occurrence was missing. The proportion of exercise-related OHCA occurring at sports arenas was 61.2% (n=164). The 30-day survival rate was 55.7% in exercise-related OHCA at sports arenas versus 30.4% in exercise-related OHCA occurring outside of sports arenas ($p<0.0001$). Characteristics and circumstances of exercise-related OHCA according to their location are presented in Table 2. Victims of exercise-related SCA at sports arenas were in general younger (mean age $\pm$ SD 57.6 $\pm$ 16.3 years compared to 60.9 $\pm$ 17.0 years, $p=0.05$) and less likely female (4.3% vs 12.2%, $p=0.02$) compared to victims of exercise-related SCA outside of sports arenas. The age adjusted odds ratio for survival at 30-days was 2.85 (95% CI 1.64-5.02; $p=0.0002$) for exercise-related OHCA at sports arenas vs exercise-related OHCA outside of arenas.

Table 2. Patient characteristics and circumstances of exercise-related OHCAs at sports arenas versus outside of sports arenas

	Sports arena	Outside of sports arena	p-value
	n=164	n= 98	
Age (mean±SD), (5,5) *	57.6 ± 16.3	60.9 ± 17.0	0.05
Females (0,0)	7 (4.3%)	12 (12.2%)	0.02
Presumed cardiac etiology (16,5)	116(78.4%)	70(75.3%)	0.64
Witness degree			
Bystander witnessed (3,8)	135(83.8%)	62(68.9%)	0.007
EMS witnessed (3,8)	9(5.6%)	11(12.2%)	0.09
Non-witnessed (3,7)	17(10.6%)	17(18.7%)	0.08
CPR			
Bystander CPR (4,3)			
Yes	144(90.0%)	54(56.8%)	<0.0001
If yes, was an AED connected before EMS-arrival? (3,0)			
Yes	42(29.8%)	6(11.1%)	0.009
If yes, was a shock delivered? (1,0)			
Yes	32(78%)	5(83.3%)	1.00
CPR by first-responders (2,2)**			
Yes	22(13.6%)	17(17.7%)	0.37
If yes, was an AED connected? (2,0)			
Yes	15(75.0%)	11(64.7%)	0.72
If yes, was a shock delivered before EMS arrival? (2,4)			
Yes	11(84.6%)	4(57.1%)	0.29
Shockable rhythm (12,4)	111(73.0%)	51(54.3%)	0.004
Delay times (medium, min)			
Collapse-call (24,20)	2.0	2.0	0.82
Collapse-CPR (13,6)	1.0	1.0	<0.0001
Collapse-defibrillation (25,211)	10.0	12.0	0.03
Outcome			
ROSC at any time (3,4)	100(62.1%)	44(46.8%)	0.02
Alive at 30 days (5,5)	88(55.7%)	28(30.4%)	<0.0001

AED, automated external defibrillation; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation; SD, standard deviation.

*Missing data

** Firefighters or police

PAPER III

In total, 9607 cases of OHCA outside of home where resuscitation was attempted occurred during the study period. The frequency of exercise-related OHCA was 6.6% (n=635). Victims of exercise-related OHCA had a significantly higher 30-day survival rate compared with victims of non-exercise-related OHCA (44.5% vs 18.8%, p<0.0001). Characteristics and factors at resuscitation in relation to exercise are presented in Table 3.

Females represented only 9.1% of the exercise-related OHCAs. Mean age did not differ significantly between male and female victims of exercise-related OHCA (59.1 years in both groups, p = 0.97). Witness degree was lower among females compared with males (66.7% vs 79.6%, p=0.03). Female victims of exercise-related OHCA received CPR by bystanders at the same frequency as males. However, median delay time from collapse to start of CPR was 1 minute longer compared with males (2.0 vs 1.0 min, p=0.001). In addition, females had a lower frequency of initial shockable rhythm (43.4% vs 64.7%, p=0.003). The 30-day survival rate was 29.3% among females compared with 46.0% among males (p=0.02). Characteristics and survival rates for exercise-related OHCA in relation to sex are presented in Table 4.

Exercise-related OHCA was stratified by age, with comparison of three different age-groups: 0-35 years of age, 36-65 years of age and > 65 years of age. The highest survival rate was found in the youngest age group, with 59.6% surviving to 30-days, compared with 46.0% among the victims aged 36-65 years and 40.4% in the oldest age group (p=0.01). Frequency of bystander witness degree and rate of bystander CPR did not differ significantly between the three groups. Shockable rhythm was more likely to occur among victims in the two younger age groups compared with victims > 65 years (66.0% and 70.1% vs 51.8%, p=0.0001). Victims of exercise-related OHCA aged 0-35 years were less frequently connected to a public AED compared to older victims (13.6% vs 34.2% and 43.9%, p=0.01). Comparison of characteristics and outcome of patients with exercise-related OHCA in different age groups are presented in table 5. A subgroup analysis of exercise-related OHCA among 0–25-year-olds identified 32 cases and 22 survivors, with a 30-day survival rate of 68.8%.

In multivariate analysis, higher age was associated with lower 30-day survival rate with OR 0.37 (95% CI 0.15 to 0.87) for age group 36-65 years and OR 0.37 (95% CI

0.14 to 0.89) for age group > 65 years, compared with age group 0-35 years. Sex did not correlate with survival. Non-witnessed exercise-related OHCA had an OR of 0.34 in comparison with bystander witnessed (95% CI 0.16 to 0.68). An association between initial shockable rhythm and higher 30-day survival rate was seen, with an OR of 2.63 (95% CI 1.61 to 4.33) compared to non-shockable rhythm. Increased delay time from collapse to start of CPR and from collapse to EMS arrival were both associated with worse prognosis. The multivariate analysis is presented in figure 4.

Table 3. Characteristics and outcome of OHCA in relation to exercise

	Exercise N=635	No exercise N=8972	p
Age (mean ±SD;years)(23,592)*	59.1±16.3	65.6±18.2	<0.0001
Sex (%) (0, 1)			
Females	9.1	26.2	<0.0001
Witnessed status (%) (15, 283)			
Crew witnessed	6.0	23.3	<0.0001
Bystander witnessed	78.4	49.8	<0.0001
Non witnessed	15.6	26.8	<0.0001
Presumed cardiac etiology (%) (33,380)	77.6	60.6	<0.0001
Initial rhythm (%) (29,359)			
Shockable (ventricular fibrillation)	62.9	29.7	<0.0001
CPR before arrival of EMS (6, 243)			
Yes	86.8	62.2	<0.0001
Delay times (median, min)			
From collapse– call (n=377, n=3077)	2	2	0.25
From collapse – CPR (n=417, n=3757)	1	2	<0.0001
From collapse–defibrillation (n=264, n=1337)	11	11	0.51
From dispatch–arrival of EMS (n=491, n=5693)	9	9	0.11
Outcome (%)			
ROSC at any time (8,223)	56.8	39.8	<0.0001
Alive at 30 days (20,254)	44.5	18.8	<0.0001

CPR: cardiopulmonary resuscitation; EMS: emergency medical services; ROSC: return of spontaneous circulation; SD: standard deviation.
*Missing data

Table 4. Characteristics and outcomes among patients with exercise-related OHCA in relation to sex

	Females N=58	Males N=577	p
Age (years; mean ± SD) (1,22) *	59.1±18.4	59.1±16.1	0.97
Witnessed status (%) (1,14)			
Crew witnessed	7.0	5.9	0.77
Bystander witnessed	66.7	79.6	0.03
Non witnessed	25.9	14.5	0.03
Presumed cardiac etiology (%) (5,28)	69.8	78.3	0.17
Initial shockable rhythm (ventricular fibrillation) (%) 5,24)	43.4	64.7	0.003
Early CPR			
a) CPR before dispatched unit? (22,271)			
Yes	86.1	87.6	0.79
If yes, was a defibrillator attached? (2,4)			
Yes	31.0	37.5	0.55
If yes, was the patient defibrillated before arrival of the dispatched unit? (0,3)			
Yes	55.6	75.0	0.24
CPR by first-responders before EMS arrival? (25,278)			
Yes	15.2	21.7	0.50
If yes, was a defibrillator attached? (0,2)			
Yes	100	82.5	0.58
If yes, was the patient defibrillated before EMS arrival? (1,0)			
Yes	60.0	76.6	0.59
Delay time (median, min)			
From collapse – call (n=30, 347)	2.0	2.0	0.65
From collapse – CPR (n=34, 383)	2.0	1.0	0.001
From collapse – defibrillation (n=14, 250)	13.5	11.0	0.22
From dispatch – arrival on scene (n=43, 448)	11.0	9.0	0.07
Outcome (%)			
ROSC at any time (1,7)	52.6	57.2	0.58
Alive at 30 days (0,20)	29.3	46.0	0.02

CPR: cardiopulmonary resuscitation; EMS: emergency medical services; ROSC: return of spontaneous circulation; SD: standard deviation.

*Missing data

Table 5. Characteristics and outcomes of exercise-related OHCA in relation to age

	0 – 35 N=53	36 – 65 N=327	> 65 N=232	p
Age (years; mean ± SD)	22.0±8.5	54.5±7.5	74.2±5.9	
Sex (%) (0,0,0) *				
Females	9.4	9.8	8.6	0.68
Witnessed status (%) (2, 4, 8)				
Crew witnessed	7.8	5.9	5.4	0.58
Bystander witnessed	72.6	79.3	78.1	0.77
Non witnessed	19.6	14.8	16.4	0.99
Presumed cardiac etiology (%) (3,16,12)	42.0	78.1	84.1	<0.0001
Initial rhythm (%) (3,13,12)				
Shockable (ventricular fibrillation)	66.0	70.1	51.8	0.0001
Early CPR				
a) CPR before dispatched unit?(24,155,100)				
Yes	86.2	87.8	87.1	0.97
If yes, was a defibrillator attached? (3,2,1)				
Yes	13.6	34.2	43.9	0.01
If yes, was the patient defibrillated before arrival of the dispatched unit? (1,1,1)				
Yes	100	70.0	73.5	0.90
b) CPR by first responders before EMS arrival? (26,159,104)				
Yes	18.5	23.2	20.3	0.12
If yes, was a defibrillator attached? (0,2,0)				
Yes	100	91.9	69.2	0.01
If yes, was the patient defibrillated before EMS arrival? (0,0,0)				
Yes	80.0	76.5	61.1	0.24
Delay time (median, min)				
From collapse–call (n=30,208,126)	2	2	2	0.02
From collapse–CPR (n=32,222,149)	1.5	1	1	0.39
From collapse–defibrillation (n=27,149,78)	11	11	10.5	0.71
From dispatch–arrival on scene (n=39,268,172)	8	10	8	0.48
Outcome (%)				
ROSC at any time (0,3,5)	69.8	54.9	57.3	0.53
Alive at 30 days (1,3,6)	59.6	46.0	40.4	0.01

CPR: cardiopulmonary resuscitation; EMS: emergency medical services; ROSC: return of spontaneous circulation; SD: standard deviation.
*Missing data.

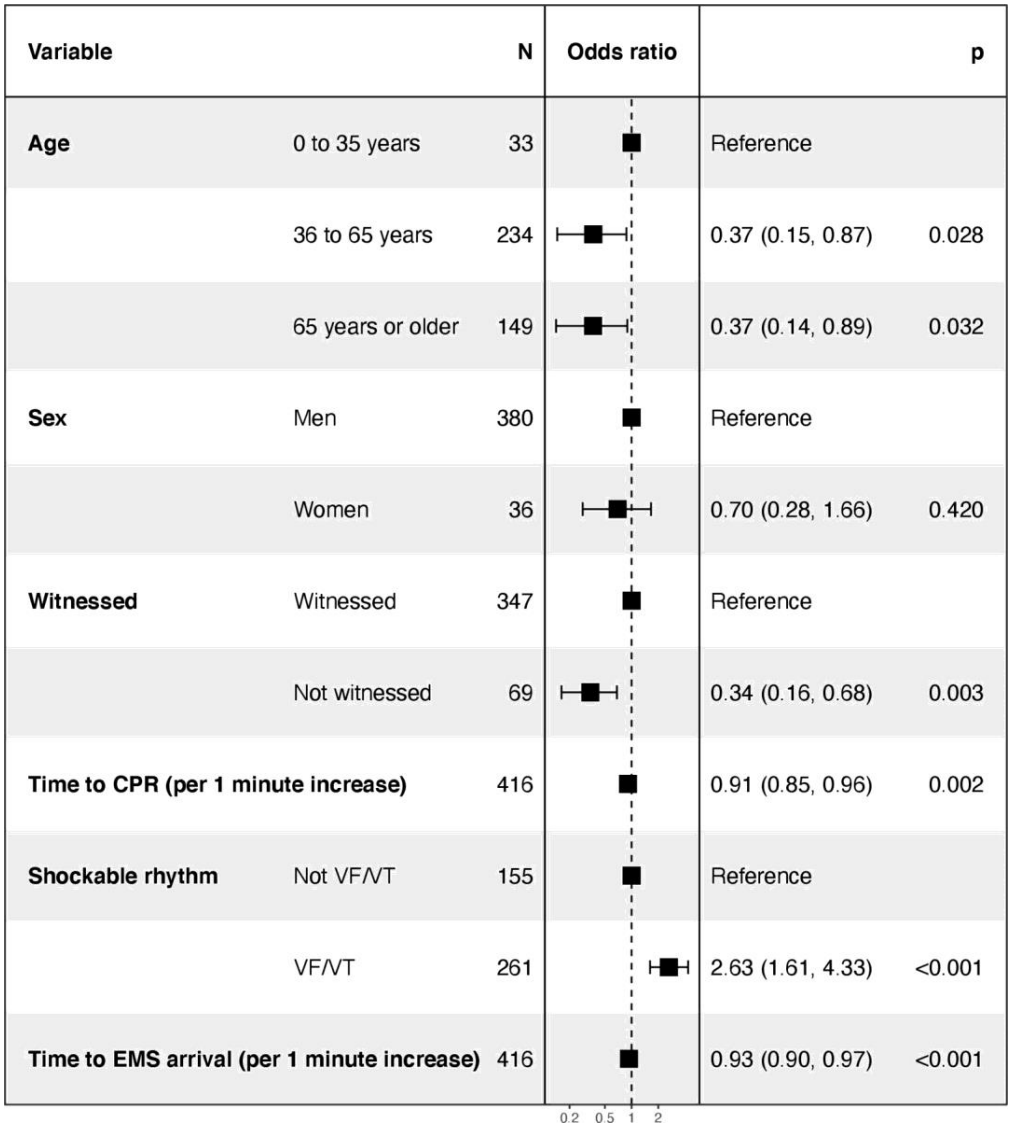


Figure 4. Forest plot with adjusted ORs for 30-day survival among exercise-related OHCA for multiple variables including age, sex, witness status, shockable rhythm, time to CPR and time to EMS arrival. CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OHCA; out-of-hospital cardiac arrest; VF/VT, ventricular fibrillation/ventricular tachycardia. Reproduced under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecomons.org/licenses/by-nc/4.0/) British Journal of Sports Medicine 2022; 56:1026-1032. http://doi.org/10.1136/bjsports-2021-105151

PAPER IV

Between 2000-2010, 149 cases of SADS were identified, accounting for 22% of all SCDs in 1–35-year-olds in Sweden during the study period. In 93% of the study subjects, an autopsy was performed, with a majority (81%) being forensic autopsies. Mean age at time of death was 22 years and there was a male predominance among SADS; 96 (64%) were males. Most of the deaths due to SADS occurred outside of hospital (n=126, 85%) and predominantly at home compared to outside of home. SADS occurred during everyday activity in 42% of cases (n=62). In 38% of cases (n =57), the SCD occurred during sleep or rest and in 12% (n=18) during physical activity. A pathological ECG prior to death was found in 18% (n=27) of SADS victims, with preexcitation being the most common pathological finding. Thirty-three percent of SADS victims, had either been hospitalized or visited an outpatient clinic within 180 days prior to death, compared with 24% in the control group (p=0.038).

Six SADS victims (4.2%) were previously hospitalized with syncope or collapse as main diagnosis, compared to three subjects (0.41%) among controls (p<0.001). Convulsion, as diagnosis at discharge from hospitalization, was found in 3.5% of SADS victims compared with 0.14% of controls (p< 0.001). Among 52% of SADS victims there was documentation of any symptoms prior to death. The most common symptom occurring <24h prior to death, was that of infectious disease (fever and/or upper airway infection), which was present in 9 % of all SADS, followed by nausea and/or vomiting, which occurred in 7%.

By search in medical records, 17 SADS subjects (11%) were found to have previous documentation of arrhythmic cardiac disease. Additionally, 6 subjects were under clinical evaluation due to suspected arrhythmia. Three had a history of a previous SCA. Psychiatric disease was identified in 17% of all cases (n=25) and documentation of use of psychotropic drugs was found in 11% of all cases (n=17).

DISCUSSION

In this thesis, we present a markedly better prognosis in exercise-related OHCA compared to non-exercise-related OHCA. Although exercise-related OHCA rarely occurs in females, they have a much worse prognosis compared to males. Younger age correlates with higher survival rates. Place of occurrence matters in exercise-related SCA, with higher survival rates seen at sports arenas compared to outside of arenas. SADS accounted for a lower proportion of SCDs in the young than previously reported in Europe. Victims of SADS were much more likely to have previous episodes of syncope or seizures, prior to death compared to controls. ECG changes, mainly preexcitation was documented frequently among SADS victims prior to death.

IMPORTANCE OF DISTINCT DEFINITIONS AND REGISTRIES WITH HIGH COVERAGE TO PRESENT ACCURATE INCIDENCE FIGURES

To determine incidence and prognosis of SCA and SCD in relation to exercise, various methodologies have previously been used. Media reports, search in medical records and EMS records as well as death certificates and often a combination of these data sources have been used, which has led to wide variations in presented incidence rates. (11, 16, 17, 19, 140-143) By strict inclusion criteria and the use of SRCR, covering the vast majority of all treated OHCAs in Sweden, we report an incidence of exercise-related OHCA of 1.2 per 100.000 person-years in the general population. However, the true incidence is most likely higher, since the proportion of OHCAs where resuscitation is not attempted should not be neglected. In a European multi-center study of OHCA, the proportion of OHCAs seen by EMS, where resuscitation was attempted was 68%. (144) Therefore, even with the use of a high-quality register, one could expect our incidence rates to be underestimated. Furthermore, we do not know the number of OHCAs where the EMS was not called upon.

HIGHER SURVIVAL RATE AMONG EXERCISE-RELATED OHCA IN THE GENERAL POPULATION

In paper I, we found significantly higher survival rates among victims of exercise-related OHCA compared to victims of non-exercise-related OHCA. This finding is consistent with studies from the Netherlands and France. (17, 19, 140) Early bystander CPR and the use of AEDs in the context of SCA during long distance running races, have previously been identified as the strongest predictors of survival. (143) We confirm that this is also the case for OHCAs in relation to exercise in the general population. Higher frequency of witness degree, bystander CPR, use of public AEDs and a higher proportion of shockable rhythm, were all factors in favor of exercise-related OHCA, compared to non-exercise-related. This observation is also in agreement with previous studies. (17, 19, 145) Victims of exercise-related OHCA were in general younger, however after adjusting for age, the 30-day survival rate was still markedly higher among exercise-related OHCA compared to non-exercise related.

In addition, the location of exercise-related OHCA correlated strongly with prognosis, as we found significantly higher survival rates in sports arenas vs outside of arenas. Victims who suffered an exercise-related SCA at sports arenas were more likely bystander witnessed compared to victims outside of arenas and impressively nine out of ten received CPR before EMS arrival. At sports arenas, victims of exercise-related SCA were more frequently connected to a public AED and had a significantly higher proportion of initial shockable rhythm compared to victims of exercise-related SCA outside of arenas. The presence of initial shockable rhythm is a strong predictor for survival in OHCA. (110, 146, 147) Herlitz *et al*. showed that documentation of VF as initial rhythm on EMS arrival was associated with a sixfold increase in survival in OHCA. (148) Another finding in our study was that the median delay time from collapse to start of CPR and from collapse to defibrillation also differed significantly in favor of sports arenas. However, even at sports arenas only one third of victims experiencing an exercise-related SCA were connected to a public AED and the median delay time from collapse to defibrillation was 10 minutes. In comparison, Marijon *et al.* found the AED use to be less than 1% in exercise-related SCA at sport facilities in France, associated with much lower survival rates compared to our study. (149)

Several studies support the safety and positive effects on SCA survival with the use of public AEDs in different settings, such as airplanes, airports, schools and in exercise-facilities as well. (121, 124, 125, 127, 150) There has been a significant increase in the number of public AEDs over the years. (126, 151) However, the frequency of public AED use remains low (121, 152, 153), which as mentioned above, was also the case for exercise-related SCA in this thesis.

Strikingly, in paper III only a minority of the youngest (age group 0-35 years) were connected to a public AED before EMS arrival, and the median delay time to defibrillation was > 10 minutes. Despite this, survival rates were remarkably high in this age group. One could only imagine what the survival rates could have been if shocks had been delivered sooner. Indeed, in a study of SCA among young football players, survival rates reached 85% when prompt CPR was performed by trained staff and an AED was used before EMS arrival. (27) Even more impressive are the results from a Japanese study, in which mobile units equipped with AEDs were implemented to provide resuscitation during road running races. Twenty-eight witnessed cases of SCA occurred during the study period. The median delay time to start of CPR was 0.8 minutes and the median delay time to delivery of the first AED shock was 2.2 minutes. The frequency of initial shockable rhythm was 86% and the survival rate was 100%! (154)

In other words, merely increasing the number of AEDs in public locations and specifically sports facilities, is not enough. A more widespread implementation of emergency action plans to increase preparedness for cardiac emergencies could increase survival even further. (127) Increased knowledge in CPR and AED use on a community level is associated with improved survival rates in OHCA. (118, 155) By introducing regular training in CPR and AED use in schools and sports clubs, we could ensure a higher level of SCA preparedness. The utilization of CPR-trained volunteers, dispatched trough specific mobile apps have also shown promising results in terms of increased rates of bystander CPR and associated better outcome of OHCA. (156-158) A combination of different approaches to reach the goals of early CPR and defibrillation is likely the key to increase survival in exercise-related SCA as well as SCA in general.

LOW SURVIVAL RATES AMONG FEMALES

Females accounted for a very low proportion of all exercise-related OHCAs, which is consistent with previous data. (17, 25, 159) This sex difference is even more pronounced than the higher overall incidence rate of SCA/SCD seen in males versus females. (17, 25) Even though rare, we found a markedly worse prognosis among female victims of exercise-related cardiac arrest compared to males. However, this finding is not exclusively seen in exercise-related cardiac arrest, but in general for female victims of OHCA. (160, 161)

A multivariate regression analysis in paper III showed that initial shockable rhythm was associated with a higher 30-day survival rate compared to non-shockable rhythm and for each minute of delayed CPR, the prognosis worsened. Female sex did not itself correlate significantly with a worse prognosis in the multivariate regression analysis. However, female victims of exercise-related SCA had a significantly longer delay to CPR and a lower frequency of initial shockable rhythm, compared to males. Since the likelihood of finding an initial shockable rhythm decreases with time to CPR and connection of a defibrillator, this finding is most likely a reflection of the delayed start of CPR in females. Another proposed explanation for the lower frequency of ventricular fibrillation among female victims of OHCA, is differences in the underlying etiology. Male victims of OHCA have been found to have a higher rate of underlying cardiac etiology and specifically underlying CAD compared to females. (162) However, we did not find a significant difference in the proportion of presumed cardiac etiology, when comparing male and female victims of exercise-related OHCA.

A surprising finding in paper II, was that the low proportion of females in exercise-related SCA, was even more pronounced at sports arenas. Unfortunately, the number of female victims was too low to adequately address the issue of frequency of and time to CPR at sports arenas in females compared with males.

In SCA, the place of occurrence naturally impacts the likelihood of bystander witnesses and thereby correlates with delayed CPR in female victims of exercise-related SCA. Marijon *et al.* found that a majority of exercise-related SCA in females occurred in the setting of individual sports rather than during team sports. While the opposite relationship between individual and team sport was seen among male victims of exercise-related SCA. (159) Hence, differences in preference for type of

sport activity between males and females could affect the likelihood of bystander presence and delay to start of CPR.

While location of occurrence and a lower rate of witness degree correlates to the delayed start of CPR seen in females, additional factors could contribute. Perman *et al*. studied attitudes towards performing CPR in females in a US population. Authors found several themes as possible obstacles for starting CPR in females: (1) that cardiac arrests in females are misinterpreted; (2) not thinking females could experience cardiac arrest at same extent as males; (3) afraid of hurting; (4) considering females fragile; (5) afraid of being accused of sexual assault and (6) the MeToo movement. (163) These attitudes are most likely not isolated to the US and could be adding to the prolonged delay to CPR in female victims of exercise-related SCA in Sweden. Interestingly, in a study by Al Dury *et al.,* which included all OHCA victims >18 years old registered in the SRCR, no significant differences in time from collapse to start of CPR, between males and females were identified. (164) The definite reason for this disparity is unknown. However, since the proportion of female victims was particularly low at sports arenas in our study, females benefitted less from the favorable circumstances of resuscitation at sports arenas compared with males. This might have enhanced the differences in delay time to CPR between males and females, which was revealed in our study but not seen when including all OHCAs.

WHY IS EXERCISE-RELATED SCA SO UNCOMMON AMONG FEMALES?

We do not know the definite reason for the low frequency of female victims of exercise-related SCA in our studies. First, there is a possibility of reporting bias, i.e. that we do not recognize SCA to be exercise-related in females at the same extent as in males. Regarding risk factors, one proposed explanation is the relatively lower prevalence of CAD in females at certain age compared with males. (11, 165, 166) Furthermore, sex differences in sports motivation, competitiveness and risk taking could contribute. Even though both males and females are motivated to engage in exercise, males have been shown to be more motivated to be competitive. (167-169) Presumably, you are more likely to push yourself to the limit and neglect eventual symptoms, in a competitive setting, thereby increasing your risk of an adverse event. Another possible explanation is differences in degree of exposure to exercise, where

males have been shown to play sport more frequently both in terms of frequency and duration. (168)

SADS IN THE YOUNG

Sudden Arrhythmic Death Syndrome (SADS) is one of the most common postmortem findings among exercise-related SCD in the young. (21, 27, 31) In paper IV, we found that risk factors, preceding symptoms and pathologic ECG findings, can be detected prior to the event. One-third of SADS victims had either been hospitalized or were in contact with an outpatient health care unit within 180 days prior to SCD. This finding is consistent with previous studies showing a high frequency of previous symptoms and healthcare contacts among SADS victims. (84, 170) In addition, nearly a fifth of SADS victims had a previous pathological ECG, with preexcitation being the most prevalent finding.

Previous hospitalization due to syncope and collapse was ten times more common among SADS subjects compared with controls. Previous studies have also reported syncope as a common preceding symptom among SADS victims. (81, 170-172) Prior health care contacts and hospitalization due to convulsion was also significantly more common among victims of SADS in comparison with controls. This finding is consistent with previous studies (81, 82, 170) and in ESC guidelines on syncope from 2018, authors recommend a detailed history taking, physical examination and ECG, to evaluate and risk stratify patients presenting with suspected syncope. Exercise-related syncope, pathological ECG findings consistent with arrhythmogenic cardiac disease or preexcitation, are highlighted as examples of high risk features, which motivates thorough assessment. (173) Furthermore, patients with ion channelopathies have been shown to have a high frequency of previous episodes of seizure like activity prior to their diagnosis. (174-176) Arrhythmic induced seizures are possibly misinterpreted as epileptic and to reach a correct diagnosis of cardiac syncope, a high index of suspicion is warranted.

Infectious disease and/or gastrointestinal symptoms prior to SCD were seen in a significant proportion of SADS cases. It has previously been described that increased vagal tone as well as fever and infectious disease could trigger arrhythmias in subjects with underlying PEDs, (62, 63, 66) and our findings likely reflect a lowered threshold for arrhythmias in susceptible individuals.

PSYCHIATRIC COMORBIDITY

A previous diagnosis of psychiatric disease and prescription of psychotropic drugs were highly prevalent in the SADS group, which is consistent with a previous study from Denmark (170). Patients with a psychiatric disease have been shown to have a higher risk of SCD (177, 178) and the use of psychotropic drugs has also been identified as a risk factor for SCD. (86, 179) Even though we found a correlation between psychiatric disease and SADS, we still do not know whether a causal relationship exists. Theoretically, psychiatric disease could be a proxy for other co-morbidities or lifestyle factors with impact on SCD risk. The use of psychotropic drugs with proarrhythmic effects in subjects with underlying unknown cardiac disease is another explanation. Finally, the possible misinterpretation of cardiac symptoms as manifestations of psychiatric disease could contribute to the high frequency of psychiatric disease among patients with SADS. Regardless, the inclusion of a resting 12-lead ECG in the somatic screening, before prescription of psychotropic drugs is an appropriate recommendation.

REWRITING THE MAP OF SADS

In paper IV, we found that SADS accounted for a lower proportion of all SCDs in the young than previously been reported in Europe. Our results reflect the combination of high-quality register data and manual search in medical records and autopsy reports, as we could exclude a significant number of SCDs, otherwise classified as SADS. In comparison, Danish colleagues have presented an incidence of SCD in the young of 1.1 per 100.000 person-years, with 28% classified as primary arrhythmic (78). A meta-analysis of SCD in the young showed that structurally normal heart accounted for 35% of all SCDs in the young in Europe, while a pooled analysis of studies from the United States, showed that only 12% of all SCDs in the young were classified as primary arrhythmic. (26) These variations are indicative of not just the possible differences in etiology comparing different populations, but the impact of definitions and methodology used to classify SCD.

By detailed analysis of the SADS victims, we conclude that this is a quite heterogenic group. In some cases, there are evidence of arrhythmic cardiac disease, in our material mainly pre-excitation, as the likely cause of death. While a definite challenge, also highlighted by previous authors (170), are cases of SADS with discrete autopsy findings, however not sufficient to fulfill the diagnostic criteria of a specific

diagnosis. Finally, there are cases with no prior medical history, ECG findings, or circumstances of death pointing towards a probable cause of death. Our results support the need for improvement in the determination of a correct diagnosis in SCD cases where there are uncertainties. (180) To increase the accuracy of the diagnosis primary arrhythmic death or SADS, a standardized and focused autopsy protocol performed by a coroner specialized in cardiac diagnostics may be helpful. Adding genetic analyses could reduce the number of unexplained deaths further, since up to half of presumed SADS cases have been identified with an underlying genetic cardiac disease. (84, 85)

Preexcitation/WPW-syndrome should perhaps be separated from other conditions causing SADS, since it represents a distinct phenotype with specific ECG findings. In our study, the most common pathological ECG finding prior to SCD was preexcitation. This indicates that even asymptomatic preexcitation should be considered a high risk finding, especially if detected during cardiac screening among athletes. A substantial proportion of patients with asymptomatic preexcitation have been found to have a high-risk accessory pathway when undergoing an electrophysiology study. (70) Even though there is a low theoretical risk of SCA/SCD in patients with asymptomatic preexcitation, the risk adds up over time and could be exaggerated by engaging in high intensity physical activity**.** Another aspect is the increased prevalence of atrial fibrillation seen among well-trained athletes, especially in endurance sports. (181-183) In case of underlying preexcitation, athletes could thereby be at higher risk of ventricular fibrillation by rapid conduction of atrial fibrillation over the accessory pathway. Ablation is recommended in both competitive and recreational athletes with preexcitation and documented arrhythmias (53). However, our findings support the approach of early ablation instead of waiting for the first arrhythmic event if preexcitation is detected during preparticipation screening. (71)

IS SCREENING OF YOUNG ATHLETES MOTIVATED?

It is generally accepted to perform preparticipation screening in elite athletes. Our findings in paper IV suggest that symptoms prior to SCD could be detected among subjects at risk of SADS, as mentioned above. A detailed medical history taken as part of the screening of athletes is crucial to detect red flags, such as previous episodes of syncope or seizures, thereby guiding further clinical investigations. Historically, there have been some disparities concerning whether a 12-lead resting ECG should

be included in the screening. The European Society of Cardiology (ESC) and Australasian College of Sports and Exercise Physician recommend a 12-lead resting ECG as part of screening. (1, 184, 185) In contrast, The American Heart Association (AHA) do not endorse a routinely use of ECG as part of screening. (186)

The addition of ECG as part of the screening of athletes has been shown to be a cost-effective way to increase the sensitivity to detect cardiac conditions at increased risk of SCA/SCD. (187-189) Harmon *et al*. found that adding an ECG to screening increased the likelihood of detecting a cardiovascular condition with risk of SCD by 6 times, compared to screening without ECG. (190) Our findings in paper IV, with nearly a fifth of SADS victims having pathological ECGs documented prior to death, support the use of ECG to detect subjects at risk of SCA.

EXERCISE RELATED SCA/SCD VERSUS AGE

In paper I-II, we present a four-fold increase in survival rate for exercise related OHCA compared to non-exercise-related, when adjusting for age. The higher survival rates seen in exercise-related SCA is thereby not solely due to subjects in the exercise-group being younger. Moreover, even if survival rates are lower in the oldest age groups, they still have a much greater chance of survival compared to victims of non-exercise-related OHCA. Important to note is that victims among the exercise-related SCAs represent a selected group, since the most vulnerable and morbid individuals will mostly not make it to the gym.

Although the frequency of exercise-related SCA in the young in Sweden has been reduced by half during the last decades (21), we might be facing an increase in exercise-related SCA/SCD among older athletes. The RACER (Race Associated Cardiac Arrest Event Registry) study found an increased incidence rate of SCA among male marathon runners between 2000 to 2004 and 2005 to 2010, a possible indication that these running events nowadays tend to attract more high-risk individuals with underlying known or occult CVD. (143) The challenge is to spot these subjects before their cardiac event. In a previous study, only 15% of 35-65 years old victims of exercise-related SCA had a known cardiac condition prior to the event. (25) Similarly, most exercise-related MIs occur in subjects without previously known CAD or history of previous MI. (13)

SCREENING OF OLDER ATHLETS

Being physically unfit is an independent and major risk factor for CAD. (191, 192) Therefore, to prevent SCA/SCD, our aim should be to identify people at risk rather than advising to avoid exercise. In ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease from 2021, regular exercise is recommended for healthy individuals of all ages and for most patients with underlying cardiac disease. To guide risk stratification, both the baseline level of physical activity and the anticipated exercise intensity should be evaluated. (53) It is also recommended that middle-aged and senior individuals at least should be evaluated through established risk charts, before engaging in strenuous sports. (1) Despite these recommendations, there is no established screening procedure or systematized risk stratification of middle-aged or senior athletes in Sweden, and of course this is largely a matter of resources. Our findings, with victims of exercise-related OHCA having impressively high survival rates, even in the oldest age-group, suggests that Sweden's exercising population, regardless of age, is worth more focus in terms of SCA-prevention.

COMPARING DIFFERENT PHYSICAL ACTIVITIES AND RISK

How much a specific physical activity or type of sport stresses the cardiovascular system depends on the individual's underlying CardioRespiratory Fitness (CRF) level. A certain physical activity will not evoke the same cardiovascular demand in subjects with a high level of CRF compared to sedentary subjects. (165) Therefore, it is troublesome to compare for example an 80-year-old person playing golf with a 19-year-old person doing sprint intervals, in terms of cardiac stress or demand. In this thesis, the most common sport associated with SCA/SCD was cycling followed by gym workout/group training. This finding is likely related to exposure since these are both common forms of exercise. In general, people are spending cumulatively more time on a bicycle compared to for example alpine skiing, thereby increasing the likelihood of a SCA occurring while cycling, rather than reflecting that this is a high-risk sport.

ETHICAL CONSIDERATIONS

Patients included in the SRCR who survive to 3 months after their SCA, are routinely contacted and interviewed by a CPR coordinator as a follow-up procedure. Patients are informed that they have been included in the registry and are also given the opportunity to opt-out from further participation. Victims of SADS were identified and included in retrospect and thereby not able to consent. However, the study posed no potential harm, since the study subjects were deceased at time of inclusion.

LIMITATIONS

National registers have been used in all four papers included in this thesis. Naturally, there are some disadvantages of register-based studies. First, since these studies are observational, there is a risk of selection bias and unaccounted confounders affecting our results. Secondly, results are dependent on the quality of data reported to the registers and the amount of missing data.

Only SCA cases where resuscitation has been attempted are included in the SRCR. Hence, our results are only representative of subjects who are eligible for, and who receive, resuscitation. We are thereby underestimating the incidence of exercise-related SCA/SCD in the general population. However, this bias is not exclusive to exercise-related SCA but for all SCAs. Since we only included cases occurring outside of hospital, we are also missing cases of exercise-related SCA occurring at the emergency department or after hospital admission. We actively chose to exclude cases of OHCA occurring at home, mainly because of their generally very poor prognosis. (193, 194) However, by doing so, of course we have missed cases of exercise-related OHCAs. In addition, there is a risk of misclassification or misinterpretation of cases of SCA/SCD. For example, the variable "cardiac etiology" in the SRCR is based on a direct evaluation made by an individual health care professional, usually an EMS crew member, and is not confirmed or updated after additional clinical investigations. The definition of exercise-related is also dependent on an individual assessment made by the person filling in the SRCR form. Another limitation is that the intensity of physical activity, in relation to METs for example, is not a variable in SRCR. We also have a fair amount of missing data, especially in variables concerning delay times.

There are also specific limitations relevant for the study of the SADS cohort in Paper IV. Due to the low incidence of SADS in the general population, a prospective study approach is not applicable for both practical and ethical reasons. Autopsy reports, even though protocol based, are dependent on individual evaluations made by the coroner. When no structural anomaly was identified and the toxicology screen was negative, the cause of death was assumed to be primary arrhythmic. However, some of these deaths might still have non-cardiac causes.

Regarding generalization of our results, one must emphasize that the study population consists of a relative homogenous Caucasian population.

CONCLUSIONS

The survival rate in this thesis was significantly higher for exercise-related OHCA compared to non-exercise-related OHCA, due in part to higher frequency of witness degree, early bystander CPR and the use of public AEDs. Further studies are needed to conclude whether there exist differences in underlying disease patterns as well as co-morbidities, which could contribute to the markedly better prognosis seen in exercise-related OHCA.

Where exercise-related OHCA occurs is of great importance, with higher survival rates seen in exercise-related OHCA occurring at sports arenas. Witness degree has a strong correlation with prognosis and could in part explain these better survival rates. Surprisingly, only a minor proportion of the youngest SCA victims were connected to a public AED at sports arenas. Although the reason for this finding is unknown, it highlights a definite room for improvement.

Exercise-related OHCA rarely occurs in females but when it does, females face a much worse prognosis than males. A lesser witness degree and longer delay time to initiate CPR in female cases, correlates with lower survival rates. These findings are indicative of a need for increased knowledge and awareness of exercise-related SCA in females.

By thorough investigation and stringent methodology, the proportion of unexplained SCDs in the young can be reduced.

SADS victims had a high frequency of previous symptoms and healthcare contacts prior to death, supporting that identification of subjects at risk of SADS is possible. Episodes of syncope or seizures must be carefully evaluated, to determine whether these are symptoms of underlying cardiac disease.

Preexcitation was the most common pathological ECG finding prior to death in the SADS population. With this in mind, preexcitation (even if asymptomatic) should not be considered a benign finding.

Psychiatric disease and use of psychotropic drugs might be risk factors for SADS. Gastrointestinal symptoms and infectious disease are possible triggers of SCA/SCD in subjects with underlying vulnerability.

CLINICAL IMPLICATIONS

- Increased AED availability and a more widespread CPR education for personnel working in sport facilities, teams and schools, could increase survival of exercise-related cardiac arrest. The use of a structured medical action plan specific to each arena or event is preferred.
- Though there is still room for improvement with an increased use of AEDs at sports arenas, their comparatively excellent SCA preparedness could be used as the basis of a role model for other public environments.
- The low survival rate seen in females was unexpected and calls for action. Increased public awareness regarding SCA in females is essential to correctly identify SCAs in females and to minimize delay time to start of CPR and defibrillation. Algorithms for CPR used for educational purposes often picture a male suffering a cardiac arrest and receiving CPR. A simple way to increase awareness of SCA in females, would be to illustrate female victims of SCA more frequently.
- With increased knowledge in symptoms suggestive of underlying cardiac disease, such as syncope and convulsions, we are more likely to identify individuals at risk of SCA. Furthermore, it is important to recognize these symptoms during preparticipation screening of athletes. Such screening should also include a 12-lead ECG, to further increase the chance of identifying subjects with risk of SCA.
- The finding of preexcitation on screening even without any prior symptoms, should warrant a discussion and evaluation of the need for an invasive electrophysiology study.
- Patients with known arrhythmic disease should be aware of possible triggers for arrhythmia, such as fever and gastrointestinal disease. Health care providers should also be aware of this risk. We recommend ECG as part of the clinical evaluation of patients with arrhythmic disease, presenting with symptoms of gastrointestinal disease or infection.
- For patients presenting with symptoms of psychiatric disease, a clinical evaluation including an ECG should be part of the diagnostic work up and certainly before prescription of psychotropics.

FUTURE PERSPECTIVES

We aim to continue with a characterization of survivors of exercise-related SCA, to possibly increase knowledge in underlying mechanisms and why they have a better prognosis compared to non-exercise-related SCA.

Little is known about prognostic factors and exercise as a possible trigger for SCD among females, since there are limited data/uncommon among women. We intend to proceed with future research with focus on female athletes – exercise habits, risk factors, trends and possible differences in underlying pathology compared to males.

For the SADS cohort, we aim to proceed with genetic analyses of SADS victims, where biological material is available, to identify possible underlying hereditary cardiac diseases.

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