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Janna Kauppila

SUDDEN CARDIAC ARREST IN NONISCHEMIC HEART DISEASE

ROLE OF MEDICATION, SUBSTANCE ABUSE AND INITIAL RHYTHM

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL

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Role of medication, substance abuse and initial rhythm

Academic dissertation to be presented with the assent of the Doctoral Programme Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 10 of Oulu University Hospital, on 17 February 2023, at 12 noon

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Abstract

During sudden cardiac arrest (SCA), the heart suddenly and unexpectedly stops beating. It predominantly leads to sudden cardiac death (SCD), which is the most common mode of death in Western countries. Nonischemic heart disease (NIHD) causes about 20% of SCAs. Many factors, such as medication or substance abuse, can induce SCA in patients with heart disease. The aim of this thesis was to investigate NIHD, initial rhythm, and the use of psychotropics and alcohol as risk factors for SCA.

Studies I and II compared the initial rhythms of SCA subjects with attempted resuscitation by the emergency personnel. In study I, we reported an association between non-shockable initial rhythm and underlying NIHD in 274 subjects with SCA. In study II, the use of psychotropic medication, especially antipsychotics, was positively associated with non-shockable initial rhythm in 222 subjects.

Studies III and IV were based solely on the Fingesture population, which consists of 5,869 consecutive victims of SCD in Northern Finland during 1998–2017. In study III, 42% of 1,301 victims of SCD with NIHD had alcohol in blood at the time of death. Elevated blood alcohol level was more common in men than in women. In study IV, we reported the use of psychotropic medication in 41% of 1,404 subjects with NIHD. According to Finnish Statistics on Medicines 2018, only 12% of the general Finnish population are users of psychotropic medication.

The cause of death was determined by medico-legal autopsy in all cases, and the cause of SCA in the survivors in studies I and II was assessed by a clinical examination including echocardiography and coronary angiography. Overall, we consider the results of these studies to improve the as yet poor understanding of the causes and mechanisms of SCA.

Keywords: alcohol, asystole, nonischemic heart disease, psychotropic medication, pulseless electrical activity, sudden cardiac death

Kauppila, Janna, Sydänpysähdys ei-iskeemisessä sydänsairaudessa. Psyykenlääkkeet, päihteiden käyttö ja elvytyksen alkurytmi

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala

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Tiivistelmä

Sydänpysähdyksen aikana sydän lakkaa äkillisesti pumppaamasta. Siitä seuraa useimmiten sydänperäinen äkkikuolema, joka on yleisin kuolinsyy länsimaissa. Ei-iskeeminen sydänsairaus aiheuttaa noin 20 % sydänpysähdyksistä. Useat tekijät, kuten lääkitys tai päihteiden käyttö, voivat aiheuttaa sydänpysähdyksen sairaassa sydämessä. Tämän väitöstutkimuksen tarkoitus oli tutkia ei-iskeemistä sydänsairautta, elvytyksen alkurytmiä sekä psyykenlääkkeiden ja alkoholin käyttöä sydänpysähdyksen riskitekijöinä.

Työt I ja II vertasivat sydämen alkurytmejä sydänpysähdyksen saaneilla potilailla, joita ensihoitajat elvyttivät. Tutkimuksessa I totesimme yhteyden ei-iskettävän rytmin ja ei-iskeemisen sydänsairauden välillä 274:lla sydänpysähdyksen saaneella potilaalla. Tutkimuksessa II huomattiin psyykenlääkkeiden, erityisesti antipsykoottien, käytön olevan yhteydessä ei-iskettävään rytmiin 222 potilaalla.

Työt III ja IV perustuivat puhtaasti Fingesture-aineistoon, joka koostuu 5,869 peräkkäisestä sydänperäisen äkkikuoleman uhrista Pohjois-Suomessa vuosina 1998–2017. Tutkimuksessa III havaitsimme alkoholia veressä kuolinhetkellä 42 %:lla 1 301:sta uhrista, joilla oli ei-iskeemisen sydänsairaus. Tutkimuksessa IV totesimme, että 1 404:sta ei-iskeemistä sydänsairautta sairastaneesta uhrista 41 % käytti psyykenlääkkeitä, kun taas Suomen Lääketilaston 2018 mukaan psyykenlääkkeitä käyttää vain noin 12 % väestöstä.

Kuolinsyy varmennettiin oikeuslääketieteellisellä ruumiinavauksella kaikissa tapauksissa. Sydänpysähdyksestä selvinneillä tapahtuman syy selvitettiin kliinisellä tutkimuksella, johon kuului sydämen ultraäänitutkimus sekä sepelvaltimoiden varjoainekuvaus. Katsommekin näiden tutkimustulosten parantavan vielä puutteellista ymmärrystä sydänpysähdyksen ja sydänperäisen äkkikuoleman taustatekijöistä.

Asiasanat: alkoholi, asystole, ei-iskeeminen sydänsairaus, psyykenlääkkeet, pulssiton rytmi, sydänperäinen äkkikuolema

To friends and family

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pondered the meaning of infinity, and I gladly joined you in opening your minds to new possibilities. I thank all my dear friends for helping me get my mind off work during free time and showing interest in my field of research. I wish to give a special thanks to my multi-talented sister Juuli, who graciously lent me her apartment as a workplace during the numerous hours of information retrieval and writing. Thank you for being my unofficial grammar proofreader and also my closest friend.

Since the age of five, writing stories has been my passion. This thesis is a story of a kind – one not written for children, but for adults with curious minds. After all, as C. S. Lewis once said: “Whenever you are fed up with life, start writing: ink is the great cure for all human ills”.

Oulu, January 2023 Janna Kauppila

Abbreviations

Ca^{2+}	Calcium
CAD	Coronary artery disease
CI	Confidence interval
CM	Cardiomyopathy
CPR	Cardiopulmonary resuscitation
ECG	Electrocardiography
Fingesture	Finnish Genetic Study of Arrhythmic Events
hERG	Human Ether-à-go-go-Related Gene
ICD-10	International Classification of Diseases, Tenth Revision
K^{+}	Potassium
LQTS	Long QT syndrome
Na^{+}	Sodium
NIHD	Nonischemic heart disease
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PEA	Pulseless electrical activity
RR	Risk ratio
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Kauppila JP, Hantula A, Kortelainen ML, Pakanen L, Perkiömäki JS, Martikainen M, Huikuri HV, Junttila MJ (2018). Association of initial recorded rhythm and underlying cardiac disease in sudden cardiac arrest. *Resuscitation 122*, 76–78.

II Kauppila JP, Hantula A, Pakanen L, Perkiömäki JS, Martikainen M, Huikuri HV, Junttila MJ (2020). Association of non-shockable initial rhythm and psychotropic medication in sudden cardiac arrest. *International Journal of Cardiology Heart & Vasculature 28:100518.*

III Kauppila JP, Pakanen L, Porvari K, Vähätalo J, Holmström L, Perkiömäki JS, Huikuri HV, Junttila MJ (2021). Blood alcohol levels in Finnish victims of non-ischaemic sudden cardiac death. *Annals of medicine 53(1), 413–419.*

IV Kauppila JP, Pakanen L, Porvari K, Vähätalo J, Holmström L, Haukilahti MAE, Perkiömäki JS, Huikuri HV, Junttila MJ (2022). Use of psychotropic medication in victims of nonischemic sudden cardiac death. Submitted.

Contents

1 Introduction

Sudden cardiac arrest (SCA) is a life-threatening condition which can revert to a normal, life-sustaining rhythm either spontaneously or through resuscitation. However, in 80–90% of cases it leads to sudden cardiac death (SCD) (Sasson et al., 2010). About half of all cardiac deaths are sudden (Huikuri et al., 2001). Nonischemic heart disease (NIHD) is responsible for about 20–25% of SCDs (Hookana et al., 2011; Huikuri et al., 2001).

Many entities and lifestyle factors can induce SCA in a patient with heart disease. The use of psychotropic medication and especially antipsychotics has been associated with an increased risk for SCD in numerous studies (Honkola et al., 2012; Ray et al., 2001, 2009), but the mechanisms for this association are partly unclear. Light-to-moderate alcohol consumption might be beneficial for the heart, but chronic heavy drinking has several harmful effects on the cardiovascular system (H. A. Cooper et al., 2000; Foerster et al., 2009; Gardner & Mouton, 2015). While the association of heavy chronic or binge drinking with ischemic SCD is well established (Mukamal et al., 2005; Wannamethee & Shaper, 1992), the relationship between acute alcohol intake and risk for nonischemic SCD has not been studied before.

The initial electrocardiographic rhythm is a vital factor in surviving SCA. Asystole and pulseless electrical activity (PEA) cannot be defibrillated and are hence called non-shockable rhythms. They have a poor survival rate from SCA (Andrew et al., 2014; Bergström et al., 2018). Most of the preceding research has focused on ventricular fibrillation, which was previously the most prevalent initial rhythm at the time of SCA. To date, asystole or PEA occur in more than half of all cases of SCA (Hulleman et al., 2012).

Understanding the reasons behind SCA is an ongoing challenge. Despite recent improvements in the prevention of SCA and SCD and treatment of coronary artery disease, SCA remains a major health problem, as about half of SCAs still occur in the seemingly healthy population (Chugh, 2017; Kuriachan et al., 2015). The focus of this population-based retrospective thesis was to assess the relationship between NIHD, non-shockable initial rhythm, use of psychotropic medication, acute alcohol intake and the risk of SCA.

2 Review of the literature

2.1 Epidemiology of sudden cardiac arrest

Sudden cardiac death (SCD) accounts for about 10% of deaths both worldwide (4–5 million per year) and in Finland (5,000–7,000 per year) (Chugh, 2017; Junttila et al., 2016; Statistics Finland, 2019). Annual rates of SCD are about 350,000 in the United States and 700,000 in Europe (Chugh, 2017; C. X. Wong et al., 2019). The incidence of SCD seems to have declined over the decades (Bray et al., 2014; Maruyama et al., 2012; C. X. Wong et al., 2019), although the findings are not altogether consistent. Neutral and increasing incidences of SCD have also been reported (Herlitz et al., 2000; C. X. Wong et al., 2019). The incidence of SCD also varies greatly according to the country, reaching 50–200 annual cases per 100,000 individuals in Western countries (Gräsner et al., 2016; Junttila et al., 2016; C. X. Wong et al., 2019). Less data is available from Asian countries, but some studies have observed annual incidences of less than 50 per 100,000 (C. X. Wong et al., 2019). The mean age of sudden cardiac arrest (SCA) subjects is about 65–70 years (Axelsson et al., 2012; B. McNally et al., 2011; Sasson et al., 2010). Some studies have reported an increase in mean age, but the findings are not consistent (Chan et al., 2014; Herlitz et al., 2000; Junttila et al., 2016; Strömsöe et al., 2015). About 30% of all SCD victims are women (Axelsson et al., 2012; Gräsner et al., 2016; Haukilahti et al., 2019; Herlitz et al., 2000). In a British study of half a million adults, the annual rate of ventricular arrhythmias in the general population was reported at 0.19% (Khurshid et al., 2018).

SCA is almost always caused by a preexisting structural heart disease. In only about 5% (1.6–6.8%) of cases an underlying heart disease cannot be identified (Hookana et al., 2011; Waldmann et al., 2018). The incidence of SCA is highest in patients with a history of cardiac events. Nevertheless, these individuals comprise a minority of SCD victims. Most SCDs occur in the general, seemingly healthy population (Figure 1) (Huikuri et al., 2001). SCD is the first manifestation of heart disease in almost half of all cases (Al-Khatib et al., 2018). About 70–75% of SCDs are caused by CAD, which can also be referred to as ischemic heart disease (Hayashi et al., 2015; Myerburg & Junttila, 2012). Nonischemic heart disease (NIHD) covers all other types of heart disease and accounts for about 20–25% of SCDs (Huikuri et al., 2001). NIHD consists of various diseases, such as cardiomyopathies (CMs), myocarditis, valvular heart disease and ion channel

disorders. The incidence of ischemic SCA is declining, but the incidence of SCA from NIHD seems to have remained on the same level, and the nonischemic proportion of SCAs has increased (Bunch & White, 2005; Junttila et al., 2016; Väyrynen et al., 2011). For decades, less efforts have been made to study the risk factors of nonischemic SCA.

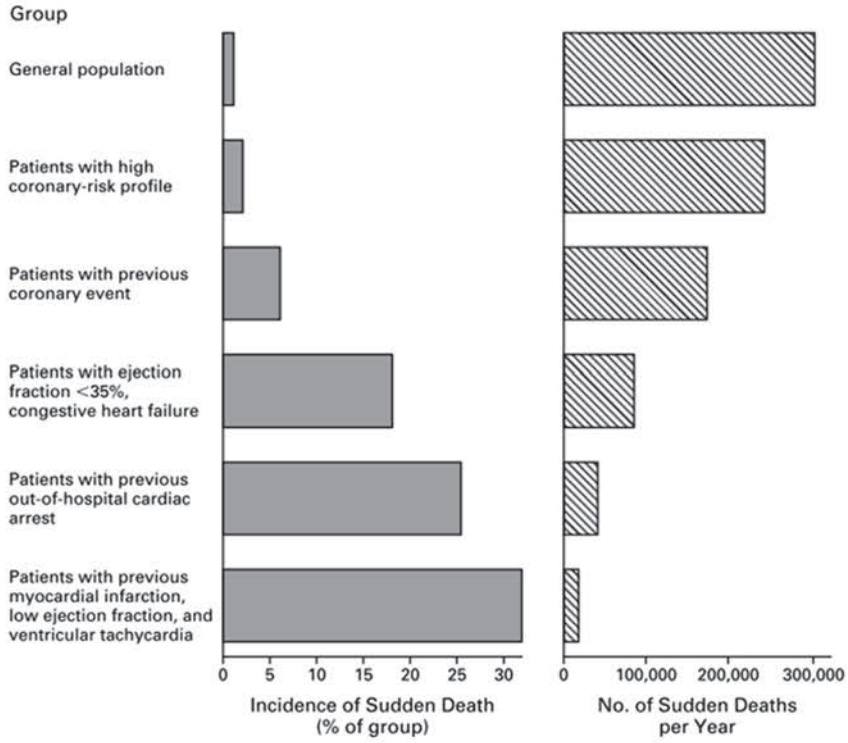

Fig. 1. Incidence of sudden cardiac death in specific populations. Reused with permission (Huikuri et al., 2001), Copyright Massachusetts Medical Society.

Approximately a quarter of all sudden deaths occur from noncardiac causes, such as drowning, trauma, pulmonary embolism, acute aortic catastrophe, stroke, sudden unexpected death in epilepsy, sepsis, drug overdose, asphyxia etc. (A. S. Kim et al., 2016; Kuisma & Alaspaa, 1997; Rea et al., 2003; Risgaard et al., 2015) Many of these conditions have been classified as SCA in some previous studies (Kuisma & Alaspaa, 1997; Kuriachan et al., 2015). However, in this thesis, SCA and SCD are defined to be of a cardiac cause, excluding all noncardiac etiologies. Many noncardiac sudden deaths may be misclassified as SCD if the cause of death is

determined only by medical history and clinical examination. This underlines the importance of autopsy confirmation in determining the cause of sudden death.

2.1.1 Survival from sudden cardiac arrest

Despite continuous efforts to improve resuscitation from SCA, the survival rates remain rather poor (Iwami et al., 2009; Sasson et al., 2010). About 20–30% of all victims of out-of-hospital SCA survive to hospital admission and 5–10% to hospital discharge (Chan et al., 2014; Gräsner et al., 2016; Teodorescu et al., 2010; M. K. Y. Wong et al., 2014; Yan et al., 2020). Favorable neurological outcome has been reported at 3.4–7.6% (Kudenchuk et al., 2012; Sinden et al., 2020). Survival from SCA seems to be lower in Asian countries compared to Western countries (Ong et al., 2015). Of out-of-hospital SCAs, 70% occur at home, which also reduces the possibility of survival (Al-Khatib et al., 2018). Factors contributing to a better survival rate are a witnessed or public arrest, short delay from the collapse to bystander cardiopulmonary resuscitation (CPR) and rhythm monitoring, initial shockable rhythm, and availability of automated external defibrillators (Al-Khatib et al., 2018). Nighttime SCA seems to have a lower survival rate compared to SCA occurring at other times of the day (L. Wang et al., 2020). Communities with a low socioeconomic status may have a lower rate of CPR during SCA and thus a lower survival rate compared to communities with a higher socioeconomic status (S. Lee et al., 2021). Women may have a slightly better prognosis from SCA than men, although there is no clear consensus (Bougouin et al., 2015; Mody et al., 2021). According to both of these meta-analyses, female victims of SCA are older and have unwitnessed arrests more often than men. Younger age seems to be independently associated with better survival from SCA (Axelsson et al., 2012; Fukuda et al., 2014).

About 60% of SCAs occur out-of-hospital and the rest inside a medical facility (Al-Khatib et al., 2018). In-hospital arrests usually have a shorter delay from collapse to resuscitation, better equipment at hand and thus a better survival rate, as about 20% of in-hospital SCAs survive to hospital discharge (Al-Khatib et al., 2018). This thesis, as do the majority of previous SCA studies, focuses on out-of-hospital cardiac arrest.

2.1.2 Initial rhythm of sudden cardiac arrest

The initial rhythm on an electrocardiography (ECG) is essential in surviving from SCA. The rhythm is identified on cardiac monitoring and it determines the course of actions during resuscitation. The electrical mechanisms of SCA can be divided into tachyarrhythmic and nontachyarrhythmic groups. The most common tachyarrhythmic rhythms are ventricular fibrillation (VF) and ventricular tachycardia (VT). The typical process of SCA evolves from VT into VF, then PEA, and finally, asystole. Due to the decrease of initial shockable rhythms during SCA, VF/VT is currently responsible for only about 25–30% cases of SCA (Bergström et al., 2018; Ko et al., 2016; Wissenberg et al., 2013). The original SCA studies observed VF/VT as the initial rhythm in over 90% of cases, and at the end of last century the proportion of VF/VT was still as high as 40–60% (Cobb et al., 2002; Goldstein et al., 1981; Herlitz et al., 2000; Holmberg et al., 2000). VT is often classified together with VF, and very limited information is available about the incidence of VT during SCA. However, VT seems to cause SCA rarely compared to VF; whether VT precedes VF in unwitnessed cardiac arrests is unknown (Goldstein et al., 1981; Greene, 1990; Väyrynen et al., 2011). Tachyarrhythmic rhythms also include atrial fibrillation, atrial flutter, sinus tachycardia and other supraventricular tachycardias. These rhythms are usually considered rather benign but can lead to SCA if left ventricular wall motion is insufficient to maintain consciousness and organ perfusion due to a rapid ventricular response rate (Brembilla-Perrot et al., 2006; Myerburg et al., 2013). In Wolff-Parkinson-White syndrome, an accessory pathway between the atria and ventricles may enable progression from atrial fibrillation to VF (Fitzsimmons et al., 2001).

The most common nontachyarrhythmic rhythms are asystole and PEA, which, according to recent studies, account for about 50–60% and 10–25% of SCA cases, respectively (Andrew et al., 2014; Bergström et al., 2018; Ko et al., 2016; Kudenchuk et al., 2012; Teodorescu et al., 2010). Asystole and PEA have been considered to associate with noncardiac causes, such as pulmonary embolism; however, they are nowadays prevalent among all causes of SCA (Kürkciyan et al., 2000). As the incidence of VF/VT is decreasing, the proportion of asystole and PEA during SCA has increased (Bergström et al., 2018; Bunch & White, 2005; Herlitz et al., 2000; Väyrynen et al., 2011). Most efforts in SCA studies have focused on VF/VT, leaving asystole and PEA with less attention. Asystole and PEA are often classified together as “non-shockable rhythms”, as they cannot be defibrillated. However, as asystole and PEA occur through distinct mechanisms and have

different survival rates, they would best be studied as separate entities. Nontachyarrhythmic rhythms also include extreme bradycardia, as well as the agonal, slow and wide QRS complexes often perceived at the end of a sustained cardiac arrest, which are not included in the definition of PEA (Myerburg et al., 2013).

Ventricular fibrillation and ventricular tachycardia

VF is a wide-complexed ventricular arrhythmia with irregular electrical activity and no organized cardiac function, as the ventricles of the heart quiver instead of contracting (Figure 2). It is characterized by a rapid ventricular rate, often more than 300 per second. Premature ventricular contractions, or ventricular extrasystoles, are prevalent in the general population, but three or more beats of ventricular origin in a row are considered as VT. VT is a wide-complexed but regular rhythm, and the ventricular rate in VT is more than 100 per minute by definition (Al-Khatib et al., 2018). Non-sustained VT continues for at least three beats but less than 30 seconds, and sustained VT lasts longer than 30 seconds. VT can be monomorphic or polymorphic, the latter containing frequent variations of the QRS axis, morphology, or both (Passman & Kadish, 2001). Torsades de pointes is a type of polymorphic tachycardia seen in patients with long QT syndrome (LQTS). Translated as “twisting of the points”, it was named after its cyclically altering appearance, and it typically beats at a rate of 160 to 250 per minute (Figure 3) (Passman & Kadish, 2001). VT rarely causes significant hemodynamical instability, but it can lead to SCA if blood flow proves insufficient for organ perfusion (Greene, 1990). VF and VT have a better outcome compared to asystole and PEA, mostly because as “shockable rhythms”, VF and VT can frequently be converted to a circulation-sustaining rhythm by defibrillation shock. Approximately 25–40% of all cases of out-of-hospital SCA with VF survive to hospital discharge (Bunch & White, 2005; Rea et al., 2003; Sasson et al., 2010; Teodorescu et al., 2013). Survival from SCA with VT can reach 65–70% according to some earlier studies (Goldstein et al., 1981; Trappe et al., 1988). Male gender and CAD are considered risk factors for VF (Alahmar et al., 2014; Greene, 1990; Teodorescu et al., 2010). Patients with VF/VT are apparently younger and more often male than those with non-shockable rhythms, and VF/VT seems to occur more often in public places (Ko et al., 2016; Teodorescu et al., 2010).

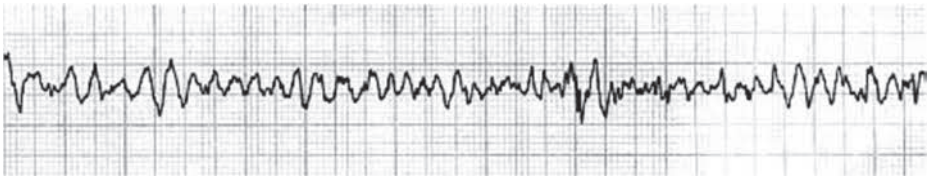

Fig. 2. Ventricular fibrillation. Reused with permission (Yap & Camm, 2003)**, Copyright BMJ Publishing Group Ltd.**

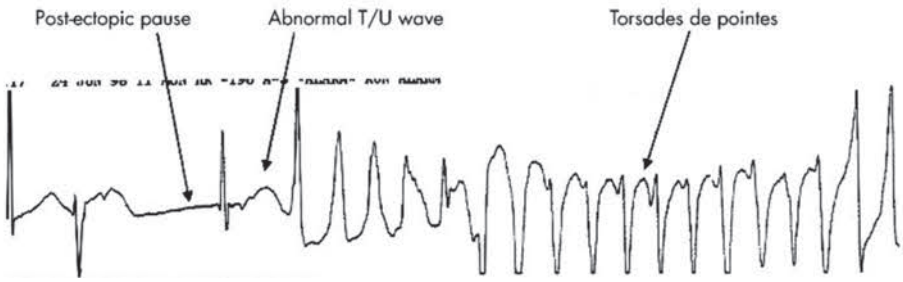

Fig. 3. Initiation of torsades de pointes. Reused with permission (Yap & Camm, 2003)**, Copyright BMJ Publishing Group Ltd.**

Asystole

Asystole is the terminal stage of SCA and eventually present in all cases of death. It means cardiac standstill without any electrical or mechanical cardiac activity. No waveform can be detected in the ECG, only an isoelectric line, hence the name "flatline", by which asystole is colloquially known. Asystole is often preceded by bradyarrhythmia or prolonged VF/VT or PEA, but asystole can also present as the first rhythm of SCA. The term "primary asystole" is typically used as a synonym for cardiac asystole, which may result from myocardial infarction or NIHD. Noncardiac or "secondary" asystole occurs because of an extracardiac reason, such as pulmonary embolism, hyperkalemia, intoxication, or neurogenic cause. This thesis focuses on cardiac asystole.

Patients with asystole seem to be more often male and younger than those with PEA, but more often female and older than those with VF/VT (Andrew et al., 2014; Bergström et al., 2018; Ko et al., 2016). The proportion of asystole during SCA appears especially high in children and adolescents, although SCA itself is rare in this age group (B. McNally et al., 2011). Asystole seems to occur at home more

often than other rhythms, which might be due to a longer delay from collapse to recording of rhythm (Andrew et al., 2014; Bergström et al., 2018; Ko et al., 2016). A small study has reported bradycardia and asystole as the mechanism of SCA in five out of six subjects with chronic kidney disease (M. C. G. Wong et al., 2015), which has been reported to increase the risk of SCD (Bilchick et al., 2012). Considering how common asystole is during SCA, it seems to be rather rare during an acute myocardial infarction (Alahmar et al., 2014). However, to our knowledge, it has not been studied before whether asystole is associated with nonischemic versus ischemic causes of SCA.

Out of all rhythms seen during SCA, asystole has the poorest outcome and also the highest rate of neurological deficits in survivors (Väyrynen et al., 2008). The survival rate from initial asystole to hospital discharge is about 1–2% with a possibility of survival with good neurological outcome of about 0.2%, with no apparent improvement over time (Andrew et al., 2014; Bergström et al., 2018; Fukuda et al., 2016; Kudenchuk et al., 2012; Teodorescu et al., 2010). The prognosis of asystole seems to be slightly better if the rhythm evolves into VF/VT during resuscitation (Luo et al., 2017). Older patients seem to have a worse prognosis from asystole: a study of 1,635 asystole cases reported no survivals over the age of 70 (Engdahl et al., 2000). Survival from asystole might be more likely in noncardiac etiologies, such as trauma, asthma, intoxication, hypothermia or near-drowning (Engdahl et al., 2000; Väyrynen et al., 2008).

Pulseless electrical activity

While no ultimate definition for PEA has been established, it is characterized by an impalpable pulse and absence of blood flow sufficient to maintain consciousness in the presence of organized cardiac electrical activity (Myerburg et al., 2013). The mechanical cardiac function can be totally absent, or some left ventricular wall motion may be detected, but it is insufficient to sustain circulation or a palpable pulse. The latter phenomenon is also known as pseudo-PEA and seems to have a better prognosis compared to PEA without any mechanical activity (C. Wu et al., 2018). PEA can be either a primary or a secondary rhythm. Unlike with asystole, the term “primary PEA” is mainly used for the initial rhythm of SCA and “secondary PEA” for a rhythm which develops from another rhythm during SCA (Myerburg et al., 2013). The latter might happen either spontaneously, or post-shock, as VF converts to PEA after a defibrillation shock. PEA can also be classified as cardiac or noncardiac, both accounting for about half of SCA cases with PEA in

previous autopsy studies (Kürkciyan et al., 1998; Virkkunen et al., 2008). Noncardiac PEA is usually categorized as secondary PEA, and it results typically from hypovolemia, trauma or obstruction to the circulation caused by conditions such as pulmonary embolism or cardiac tamponade (Kuisma & Alaspaa, 1997; Myerburg et al., 2013). Pulmonary disease seems to be an independent risk factor for noncardiac PEA, probably due to hypoxia, which has been recognized as a prevalent contributor to PEA (Teodorescu et al., 2010).

The factors behind primary cardiac PEA are not very well known. Acute myocardial infarction seems to be a frequent cause of primary PEA (Dumas et al., 2010; Virkkunen et al., 2008), whereas the association of NIHD with PEA has not been studied. Older age has been shown to associate independently with PEA, and the proportion of PEA among SCA cases increases with age (Andrew et al., 2014; Bergström et al., 2018; Engdahl et al., 2001). The prognosis of PEA is especially dismal in the elderly: one study of 1,069 cases of SCA with PEA as initial rhythm reported no patients over 80 years of age surviving to hospital discharge during the 17-year study period (Engdahl et al., 2001). Women seem to develop PEA more likely than other rhythms during SCA, but they seem to have better prognosis from PEA (Bergström et al., 2018; Ko et al., 2016; Teodorescu et al., 2012).

The survival rate to hospital discharge in SCA with PEA varies roughly between 5 and 10% (Andrew et al., 2014; Bergström et al., 2018; Engdahl et al., 2001; Ko et al., 2016; Teodorescu et al., 2010). A favorable neurological outcome is achieved in only 1–3% of PEA cases, but compared to asystole, PEA has 8-fold odds of survival (Fukuda et al., 2016; Kudenchuk et al., 2012). The prognosis of PEA seems to have improved slightly over the years, although this trend has not been demonstrated in all studies (Andrew et al., 2014). In a study of 9,168 cases of SCA with PEA, 30-day survival from PEA increased from 0% to 4.9% over the 27-year study period (Bergström et al., 2018). Kudenchuk et al have also observed increasing survival rates in nontraumatic SCAs with PEA. During the 10-year study period, survival to one year changed from 6.2% in the first five years to 11.5% in the latter five years, with an OR of 1.90 (95% confidence interval [CI] 1.27–2.85), and the neurological outcome of the participants developed similarly (Kudenchuk et al., 2012). Even with improvements, the survival rate of PEA remains far below those of shockable rhythms.

2.1.3 Resuscitation

During SCA, the victim is unresponsive without normal breathing or circulation (Buxton et al., 2006). There are usually no premonitory symptoms, as one typically loses consciousness within seconds to minutes. Sometimes nonspecific symptoms, such as palpitations, chest pain or shortness of breath might be present, especially in the event of acute cardiac ischemia. By definition, SCA occurs within an hour of the onset of symptoms (Adabag et al., 2010).

The term "chain of survival" (Figure 4) was introduced in 1991, and each link has been further developed ever since (Cummins et al., 1991). It was designed to improve the poor survival from SCA and consists of four parts: early access, early CPR, early defibrillation and early advanced cardiac life support. As the possibility of survival from VF drops by 10% with every minute without defibrillation, all links of the chain need to work properly in order for the patient to survive (Olson et al., 1989). Early access includes recognizing the situation either by the patient, if they have premonitory symptoms or a bystander, and informing the emergency medical system. Early CPR ought to be started immediately after collapse after finding a lifeless person if the victim is unconscious and not breathing regularly. If only one bystander is present, consulting the emergency medical system before initiating resuscitation is recommended to ensure minimal delay to recording of rhythm. Basic adult CPR consists of 30 chest compressions followed by two ventilations, either by mouth or using a bag-mask ventilator (Panchal et al., 2020). Without CPR, SCA starts causing irreversible brain damage after only a couple of minutes (Sinden et al., 2020). CPR may temporarily generate enough blood flow to prevent permanent brain damage and death during SCA, but even with well-performed CPR, the likelihood of survival and neurological intactness start to decrease in a prolonged arrest (Bircher et al., 2019; Iwami et al., 2009). Bystander CPR, which is performed by a person who is not part of the emergency response team, is administered in 20–60% of SCA cases (Axelsson et al., 2012; Jacobs et al., 2004; Sasson et al., 2010; Strömsöe et al., 2015; Yu et al., 2020). Bystander CPR has been associated with a 2- to 3-fold increase in survival especially in cases of shockable rhythm, thus remaining the most effective link in the chain of survival (Axelsson et al., 2012; Leong, 2011; Sasson et al., 2010; Song et al., 2018). Community interventions for basic life support have increased the rates of bystander CPR and use of automated external defibrillators, and these changes have proven successful with a pooled OR 1.3 for survival compared to communities with no interventions (Yu et al., 2020). Similar findings have been reported from

interventions for health-care professionals (Lockey et al., 2018; Strömsöe et al., 2015). Nevertheless, the proportion of subjects who received CPR, along with the overall survival from out-of-hospital SCA, has plateaued in the recent years (Panchal et al., 2020; Virani et al., 2020).

Early defibrillation is usually administered by emergency personnel. However, many facilities and individuals nowadays have access to automated external defibrillators, which can be used by lay people as well. Defibrillation can only be performed if the cardiac monitor shows a shockable rhythm, i.e., VF or VT. Shockable rhythms rarely revert spontaneously without CPR and defibrillation. Adding defibrillation to CPR seems to increase survival with a risk ratio (RR) of 1.3, but whether the defibrillation is performed immediately or after short CPR seems to have no effect on survival (Sanna et al., 2008; Simpson et al., 2010). Average response time from call to emergency medical team arrival is typically 5–8 minutes in urban areas (Axelsson et al., 2012; Sasson et al., 2010; Strömsöe et al., 2015). According to the 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, rhythm check and defibrillation ought to be repeated every two minutes if a shockable rhythm persists, and CPR should be resumed immediately after the shock until the next rhythm analysis and shock (Panchal et al., 2020).

Fig. 4. The chain of survival from sudden cardiac arrest. Reused with the permission of Wolters Kluwer Health, Inc (Cummins et al., 1991)**. CPR = cardiopulmonary resuscitation.**

Early advanced cardiac life support includes securing the airways by tracheal intubation or a supraglottic airway, as well as using intravenous medications. After securing the airways, 100% oxygen and continuous waveform capnography can be used. Sometimes an ultrasound scan or measurement of arterial blood gases are performed during CPR, although the benefit is uncertain (Panchal et al., 2020).

Intravenous adrenaline should be given immediately after recognizing a non-shockable rhythm and repeated every 3–5 minutes (Panchal et al., 2020). In case of a shockable rhythm, intravenous adrenaline is given every 3–5 minutes after two unsuccessful defibrillations, and intravenous amiodarone or lidocaine is given after three unsuccessful defibrillations (Panchal et al., 2020). In a recent meta-analysis, standard-dose adrenaline improved survival to hospital discharge compared to placebo with a RR of 1.4, but it did not improve the neurologic outcome of survivors (Aves et al., 2020). Amiodarone has been reported to improve survival to hospital admission compared to placebo with an OR of 1.6 (Kudenchuk et al., 1999). Reversible causes, such as hypoxia, hypovolemia, hypo/hyperkalemia, hypothermia, acidosis, tension pneumothorax, cardiac tamponade, toxins and pulmonary/coronary thrombosis should be identified and, if possible, treated during resuscitation (Panchal et al., 2020).

The goal of resuscitation is the return of spontaneous circulation, which often manifests as breathing, coughing or movement (Jacobs et al., 2004). Post-resuscitation care focuses on optimizing cardiopulmonary function and organ perfusion, monitoring vital signs such as blood pressure, pulse, temperature and oxygen saturation, and treating reversible causes. Consciousness is not always obtained immediately, as the patient may remain comatose for a period of time after the incident. In some cases, especially those with VF/VT as the initial rhythm, the patient's body temperature is temporarily lowered in order to achieve a better neurologic outcome (Calabró et al., 2019). Myocardial infarction causes the majority of SCAs, and coronary angiography is thus usually performed in cases with VF and/or ST-segment elevation in post-resuscitation ECG; however, myocardial infarction is also common in cases with no obvious non-cardiac cause of arrest (Millin et al., 2016; Panchal et al., 2020; Soar et al., 2021). Echocardiography, ECG, radiologic imaging, laboratory analyses etc. are administered to detect cardiac and non-cardiac causes behind the arrest. SCA is a serious life-threatening situation, and even after successful resuscitation the patient must be closely monitored. Implantable cardioverter-defibrillators automatically deliver a shock in case of a recurring VF/VT, and they are implanted in cases with no reversible cause for the incident (Gregoratos et al., 2002). Long-term effects on mental health and quality of life are prevalent in SCA survivors and their families, as one third of SCA survivors experience depression, anxiety, or post-traumatic stress (Panchal et al., 2020).

In most cases of SCA, resuscitation is eventually pronounced unsuccessful and terminated. Medical futility is a term used in cases of SCA in which treatment

provides minimal or no chance of survival, usually less than 1%; which is, interestingly enough, approximately the survival rate of asystole (Väyrynen et al., 2008). According to the 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, resuscitation should not be attempted if early or late postmortem signs, such as cooling of body temperature, postmortem lividity, muscle rigidity or decomposition are present. In unwitnessed arrests, resuscitation should be withheld if bystander CPR is not performed, return of spontaneous circulation is not obtained, and defibrillation shocks are not given before transport (Panchal et al., 2020). If an arrest is witnessed by a layperson, the same rules apply, with the exception that bystander CPR does not affect the decision. Otherwise, the patient ought to be transported to a hospital and examined by a physician. According to Finnish Current Care Guidelines for Resuscitation 2016, termination of resuscitation should be considered after 20 minutes in cases of PEA and asystole, if VF/VT or return of spontaneous circulation is not even momentarily obtained and hypothermia or other reversible cause of arrest cannot be identified (Skrifvars et al., 2010; Working group appointed by the Finnish Medical Society Duodecim, the Finnish Resuscitation Council, the Finnish Society of Anaesthesiologists, the Finnish Red Cross, 2016). In case of VF/VT, Finnish guidelines recommend consideration of termination after 40 minutes if return of spontaneous circulation is not achieved, collapse was not witnessed by emergency personnel, and no reversible cause can be identified.

2.2 Mechanisms of sudden cardiac arrest

2.2.1 Cardiac conduction system and electrocardiography

The cardiac conduction system consists of various nodes and specialized pacemaker cells which initiate and coordinate the cardiac contractions required to sufficiently pump blood throughout the body. A wave of depolarization and repolarization of all of the heart's muscle cells, or cardiomyocytes, forms the basis for the contraction and relaxation of the heart. Action potential equals the rapid rise and successive fall of membrane potential which enables the contraction of cardiomyocytes. Cardiac action potential consists of five phases (0–5) illustrated in Figure 5. The electrochemical changes are mostly based on sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}) ion currents in and out of the cells. Differences in the concentrations of ions in extracellular matrix and intracellular fluid, or

cytoplasm, constitute a resting membrane potential of -90 mV (phase 4), as the cytoplasm has a negative electric charge compared to the extracellular matrix. A cardiomyocyte depolarizes when the transmembrane potential reaches -60 – -70 mV resulting from a fast inward Na^+ flow (phase 0) (Kennedy et al., 2016).

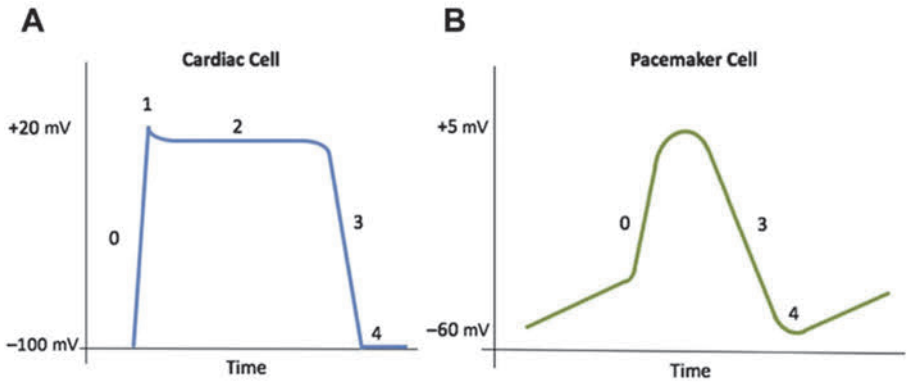

Fig. 5. (A) Normal cardiomyocyte action potential. (B) Pacemaker cell action potential. Reused with the permission of Elsevier (Kennedy et al., 2016).

The wave of depolarization first travels through the atrial myocardium, causing the atria to contract. Bachmann's bundle delivers the signal to the left atrium, which contracts slightly after the right atrium. After depolarizing the atria, the signal then reaches the atrioventricular node, which is the only pathway between the atria and the ventricles. It causes a delay of about 0.12 seconds, which enables the atria to fill with blood before the next contraction. This delay also plays an important role in rapid atrial arrhythmias, such as atrial fibrillation, as it blocks some of the signals and helps maintain a slower ventricular response rate (Kennedy et al., 2016). From the atrioventricular node, the impulse continues to the bundle of His, is divided to left and right bundle branches, and finally subdivides into Purkinje fibers, beginning the depolarization of the ventricles. The septum is depolarized first, after which the signal moves from the apex of the heart to the base, enhancing a structured contraction towards the aorta and pulmonary arteries. Early rapid repolarization and a plateau phase (phases 1–2), during which the membrane potential is about +20 mV, follows (Kennedy et al., 2016). During the plateau phase, a cell is virtually unable to contract before reaching its resting state, preventing excessive contractions and resulting in effective cardiac function (Kennedy et al., 2016). After the plateau phase, a closing of Ca^{2+} and opening of K^+ channels causes

the cell to repolarize (phase 3) and return to its resting potential (Kennedy et al., 2016). One of these K^+ channels is the human ether-à-go-go-related gene (hERG) channel, which conducts the rapid delayed K^+ rectifier current (Grant, 2009). Blockage of this channel, either by congenital or acquired causes, causes QT prolongation (Thomas et al., 2006). The conduction system is illustrated in Figure 6.

Pacemaker cells are unique, as they do not contract and thus do not have a plateau phase but only phases 0, 3 and 4. Normal cardiomyocytes can only depolarize due to an external stimulus, whereas pacemaker cells slowly depolarize themselves and are thus able to maintain a stable heart beat spontaneously (DiFrancesco, 1993; Kennedy et al., 2016). This phenomenon is known as slow diastolic depolarization. A slowing outward current of K^+ and an inward Na^+ current raise the membrane potential up to a threshold of -40 – -50 mV, after which a slow Ca^{2+} channel opens and the depolarization of pacemaker cells (phase 0) begins (Bartos et al., 2015; DiFrancesco, 1993).

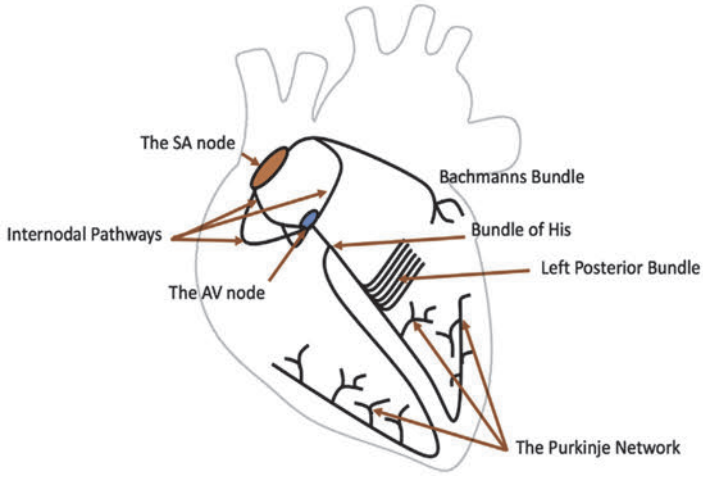

Fig. 6. The cardiac conduction system. Reused with the permission of Elsevier (Kennedy et al., 2016)**. AV = atrioventricular, SA = sinoatrial.**

If the sinoatrial pacemaker is nonfunctional or slowed or an atrioventricular block is present, an ectopic escape beat is generated in the more distal pacemaker cells along the conduction system. A junctional escape beat is formed in the atrioventricular junction and fires at a pace of 40–60 beats per minute. A ventricular escape beat is slower than 40 per minute and is generated in the bundle branches or

Purkinje fibers (Kennedy et al., 2016). The sinoatrial node has a shorter repolarization phase (phase 4) compared to the more distal pacemaker cells, as it fires at a rate of 60–100 beats per minute (Kennedy et al., 2016). According to a leading hypothesis, this intrinsic heart rate is predominantly managed by a mixed inward Na^+/K^+, or ”funny” current (Bartos et al., 2015; DiFrancesco, 1993). The autonomic nervous system also impacts the heart rate, as sympathetic stimulation accelerates and parasympathetic decelerates it. The intrinsic heart rate can be detected by eliminating the effect of autonomic regulation by administering a large dose of atropine and beta-blocker, which, according to a landmark study, results in a heartbeat of about 80–120 beats per minute (Jose & Collison, 1970). With autonomic regulation, a normal resting heart rate is between 40 and 100, predominantly 60–70 beats per minute.

The electrical cardiac function is often illustrated with an ECG (Figure 7). The basic ECG consists of 12 leads and thus provides 12 views of the heart. The P wave marks the depolarization of the atria. The QRS complex represents the depolarization of the ventricles. The repolarization of the atria can not be seen on ECG as it is hidden behind the QRS complex. The repolarization of the ventricles is marked by the T wave. The QT interval is measured from the start of the Q wave to the end of the T wave. Corrected QT interval can be calculated using a person’s heart rate. It enables comparisons of QT values by adjusting them to match a heart rate of 60 per minute. Normal corrected QT time is usually defined as ≤ 460 ms for women and ≤ 440 ms for men (Witchel et al., 2003). A lengthened QT interval, due to either acquired causes or inherited LQTS, is a risk factor for SCA (Kallergis et al., 2012). A QT interval of 600 ms causes an absolute arrhythmia risk of 25 in 100,000 and a 2.76-fold increased risk compared to a QT interval of 400 ms (Beach et al., 2018).

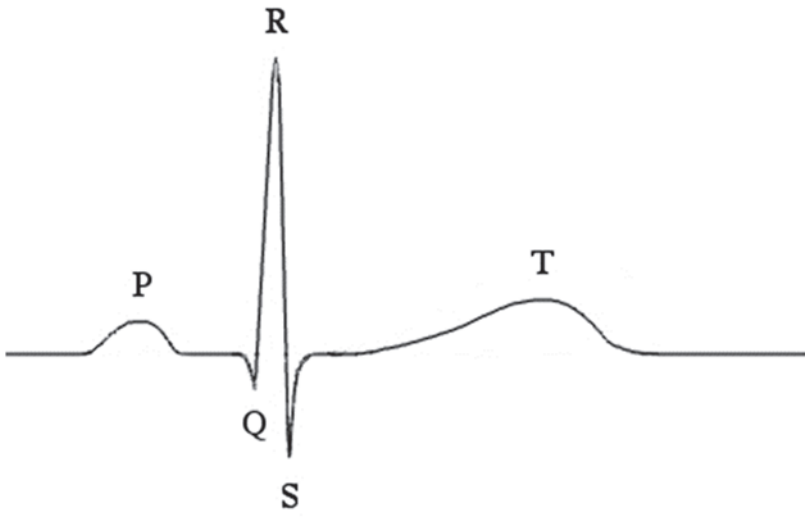

Fig. 7. Normal electrocardiography.

A normal cycle of mechanical cardiac function consists of two phases, systole and diastole. During diastole, as cardiomyocytes relax, the atria and ventricles fill with blood. The contraction of atria occurs at the end of diastole. The contraction of the left and right ventricle marks the beginning of mechanical systole. During the contractions, the four heart valves – mitral, aortic, tricuspid and pulmonary valve – keep the blood from flowing backwards. The function of the left ventricle is the most essential of all chambers, as its sufficient cardiac output maintains the delivery of oxygen-rich blood to all organs and tissues. The left ventricle faces the highest workload and thus has the thickest muscular wall of the four chambers. From the left ventricle, oxygen-rich blood flows through the aorta into the peripheral circulation and coronary arteries. Superior and inferior vena cava collect the deoxygenated blood and funnel it back towards the heart, into the right atrium and right ventricle. Pulmonary circulation then follows, as blood is replenished with oxygen in the lungs. Pulmonary veins return the blood back to the left atrium and the cycle is repeated. Electrical and mechanical cardiac function are closely integrated. During PEA, however, electrical activity seen on an ECG monitor may seem like a normal sinus rhythm, but mechanical cardiac function is absent.

2.2.2 Initiation of fatal arrhythmia

The initiation of lethal arrhythmia and SCA requires three components: a transient risk factor, a trigger, and a substrate. Transient risk factors temporarily expose the patient to a higher risk for SCA. Acute cardiac ischemia and myocardial infarction are common transient risk factors in patients with CAD. Acute cardiac ischemia, commonly known as a heart attack, rapidly affects the electrophysiological characteristics of cardiomyocytes. Alterations in the refractoriness, conduction and automaticity of myocytes all increase the possibility of ventricular arrhythmias (Janse & Wit, 1989). Factors such as electrolyte abnormalities (e.g. hypokalemia, hyperkalemia or hypomagnesemia), reduced left ventricular ejection fraction, metabolic or respiratory acidosis, and increased sympathetic activity may contribute to the event; however, they may also act as transient risk factors for SCA without acute ischemia (McElwee et al., 2016).

Medications can act as transient risk factors and thus predispose an individual to arrhythmias via different mechanisms. QT-prolonging medications, such as most psychotropics, antiarrhythmics, antimicrobials and antihistamines, may increase the risk of polymorphic VT, which can lead to VF and SCA. At the cellular lever, this is caused by blockades in K^+ currents which prolong the action potential (Yap & Camm, 2003). Antidepressants and antipsychotics have also been reported to induce K^+ and Ca^{2+} channel inhibition in the myocardium, which may cause hypotension and arrhythmias (Park et al., 1999). Alcohol is a toxin to cardiomyocytes and can in high concentrations cause cell damage and oxidative stress, resulting in contractile failure. Acute alcohol intake also reduces left ventricular ejection fraction and increases blood pressure and sympathetic nervous system activity, promoting arrhythmias and SCA (Gardner & Mouton, 2015). Illicit drugs, most notably cocaine, can prolong the QT interval and affect multiple types of ion channels (Phillips et al., 2009).

SCA is typically triggered by premature ventricular contractions, which occur sporadically in nearly all people and are often benign. They are, however, considered to be a risk factor for SCA, as they can trigger arrhythmias at least in patients with preexisting heart disease (Ataklte et al., 2013). Premature beats are more common in patients with cardiovascular disease, such as hypertrophic CM or acute myocardial infarction (Adabag et al., 2010; Heidbüchel et al., 1994). In some cases, premature atrial contractions can also act as the trigger for SCA (Takahashi et al., 2021).

The substrate is a factor which maintains the arrhythmia. Reentry is the most common substrate (Gaztañaga et al., 2012). Reentrant VF or VT occurs when the heart's electric signal fails to travel the normal depolarization circuit from the sinoatrial node to the atria and ventricles, but instead takes an alternative route back upon itself, creating an abnormal, rapid loop and tachycardia. Anatomical, or classic reentry results when the electric impulse starts circling around an anatomical obstacle, such as an area of slowed conduction due to myocardial damage. As this area is not depolarized, it can reexcite previously depolarized areas and thus initiate reentry. Functional reentry is caused by heterogeneities in repolarization and other electrophysiologic characteristics of the myocardium (Antzelevitch & Burashnikov, 2011; Gaztañaga et al., 2012). In addition to reentry, the substrate can also be enhanced automaticity or triggered activity. Automaticity is the ability of a cardiomyocyte to spontaneously depolarize, which means that the impulse is not conducted from other myocytes. Although this is a normal phenomenon in pacemaker cells, and also possible for any cardiomyocyte at a low enough heart rate, enhanced automaticity in pacemaker cells or abnormal automaticity in other cardiomyocytes can lead to tachyarrhythmia. In triggered activity, changes in intracellular Ca^{2+} concentration provoke premature ventricular contractions and arrhythmia (Wolf & Berul, 2008).

The substrate varies according to the type of heart disease. In structural heart disease, such as CAD and nonischemic CMs, the substrate is typically an area of slowed conduction caused by myocardial damage. These areas enable anatomical reentry (Ghuran & Camm, 2001). Heart failure can act as a substrate even without myocardial scarring (B. A. Steinberg et al., 2017). In ion channel disorders, such as LQTS or Brugada syndrome, the arrhythmia usually perseveres because of the heterogeneity of myocardial repolarization, which sustains functional reentry and tachycardia (Wolf & Berul, 2008). Enhanced automaticity is often present in more benign rhythms, such as sinus tachycardia, atrial fibrillation and supraventricular tachycardia. Catecholaminergic polymorphic VT is an example of triggered activity, as delayed afterpolarizations induce polymorphic tachycardia (Baltogiannis et al., 2019). Another example is torsades de pointes, in which early afterdepolarizations during phases 2–3 lead to the rapid arrhythmia (El-Sherif et al., 2019).

The mechanisms covered above apply predominantly to tachyarrhythmias, such as VF and VT. Asystole and PEA have received less attention in studies concerning the mechanisms of SCA. Primary asystole occurs due to a failure of the cardiac conduction system. The conduction failure is typically a third-degree atrioventricular block, i.e., complete loss of conduction between the atria and

ventricles, during which P-waves are often present. Eventually it progresses into asystole, if subsidiary pacemaking fails (Da Costa et al., 2002). Various factors, such as medications, electrolyte disorders and metabolic factors, can induce conduction disturbances and thus contribute to asystole (Hsu et al., 2003; Zeltser et al., 2004). In secondary, or noncardiac asystole, an extracardiac factor results in a failure to generate depolarization, and hypoxia and metabolic acidosis often contribute to the incident. Ictal, or seizure-induced asystole, is a rare example of neurogenic asystole mostly seen in temporal lobe epilepsy, during which a parasympathetic vasovagal response and autonomic dysregulation are thought to trigger the collapse (Tényi et al., 2017). In rare cases, the trigeminus nerve may prompt the trigeminocardiac reflex and cause asystole during craniofacial surgery (Sandu et al., 2017).

The key mechanism for the initiation of primary PEA is a contractile failure of the myocardium in the presence of organized cardiac electrical activity (Myerburg et al., 2013). Intracellular Ca^{2+} concentration is vital in adjusting myocardial contractions (Bode et al., 2011). Metabolic stress is often present in chronic heart failure due to CAD or NIHD (Stanley et al., 2005), and changes in Ca^{2+} concentrations and other metabolic factors might thus increase the risk of contractile dysfunction and PEA in patients with heart failure. Parasympathetic activity has been proposed as a transient risk factor for primary PEA in a canine model in which chemical or surgical vagotomy was performed on animals with asphyxia-induced PEA (DeBehnke, 1993). Return of spontaneous circulation was achieved in 13% of no vagotomy animals and in 75% of vagotomy animals ($n = 16$, $p = 0.02$). Some other hypotheses for the development of PEA have been suggested, concerning innate immunity, inflammatory cytokines, hormones, and Ca^{2+} channel inhibition (Myerburg et al., 2013). All in all, information about the mechanisms initiating asystole and PEA is scarce.

2.3 Causes of sudden cardiac arrest

2.3.1 Ischemic heart disease

CAD is the most common type of heart disease and the leading cause of death worldwide (GBD 2013 Mortality and Causes of Death Collaborators, 2015; James et al., 2018). The prevalence of CAD is about 6,400 in 100,000 US adults ≥ 20 years (Go et al., 2013). The etiology of CAD is multifactorial, with genetic

susceptibility as well as clinical risk factors contributing to the pathogenesis. The main established independent risk factors of CAD, with odds ratios (ORs) for myocardial infarction from the INTERHEART study, are as follows: smoking (OR 2.9), obesity (OR 1.6), hypercholesterolemia (OR 3.3 for raised ApoB/ApoA1 ratio), hypertension (OR 1.9) and diabetes (OR 2.4) (Yusuf et al., 2004). Most CAD patients have at least one clinical risk factor (Vasan et al., 2005). Other risk factors for CAD include rheumatoid arthritis, chronic kidney disease and non-alcoholic fatty liver disease (D. Kim et al., 2012; Manjunath et al., 2003; Maradit-Kremers et al., 2005). CAD is caused by atherosclerosis, i.e., accumulation of lipoproteins in the intima, the innermost layer of coronary arteries. While atherosclerosis is present to some extent in all adults (Strong et al., 1999), over time, it may cause thickening and narrowing of the vessels, and in some cases, abrupt plaque rupture and occlusion resulting in myocardial infarction. If not rapidly treated, myocardial infarction can lead to chronic heart failure or even SCD (Roger, 2013). The clinical manifestations of CAD also include stable and unstable angina pectoris (i.e., chest pain or discomfort). Both chronic and acute symptoms, such as chest pain, dyspnea and fatigue, are induced by myocardial ischemia, i.e., a shortage of oxygen caused by reduction of blood flow in the diseased arteries. Typical stable angina pectoris occurs during exercise and ceases within minutes of pausing or administrating nitroglycerin (Cassar et al., 2009).

Coronary vasospasm is a rather rare, transient, reversible contraction of coronary arteries, which can cause typical or atypical chest pain and myocardial ischemia with or without CAD (Lanza et al., 2011). Coronary vasospasm may in some cases cause myocardial infarction and SCA (Waldmann et al., 2017), and it is a possible cause of SCD in victims with a normal heart in autopsy (Igarashi et al., 1993).

2.3.2 Nonischemic heart disease

Cardiomyopathies

CMs are a heterogeneous group of diseases of the heart muscle, characterized by progressive structural changes, such as fatty or fibrotic infiltration, hypertrophy, chamber dilation and left ventricular dysfunction (Braunwald, 2017). These changes may eventually lead to heart failure and non-sudden or SCD (Braunwald, 2017; Pimentel et al., 2017). The definition of CM has changed over the past few

decades. The first 1980 WHO/ISFC classification defined CMs as dilated, hypertrophic and restrictive (Chazov et al., 1980). In the 1995 revision, right ventricular arrhythmogenic CM was added to the list (Richardson et al., 1996). Simultaneously, the term "specific cardiomyopathies" was introduced. Some diseases included were ischemic, valvular, hypertensive, inflammatory and metabolic CM. Discussion arose, claiming the definition of CM to be unnecessarily broadened by this classification (Thiene et al., 2008). The 2006 AHA scientific statement described CMs as frequently genetic and categorized them as primary and secondary, primary meaning genetic and acquired diseases predominantly confined to the myocardium (Maron et al., 2006). Diseases with mere electrical changes and a structurally normal heart, such as inherited channelopathies, were also viewed as primary CMs. Secondary CMs included those of systemic causes, such as sarcoidosis, amyloidosis, drugs, diabetes, hypothyroidism, rheumatoid arthritis and nutritional deficiencies. The 2007 ESC position statement defined CMs as diseases of the heart muscle with structural and functional abnormalities without hypertension, CAD, valvular heart disease or congenital heart defect which would sufficiently explain the abnormalities (Elliott et al., 2008). CMs were classified as dilated, hypertrophic, restrictive, arrhythmogenic and unclassified. This classification is perhaps applied the most. However, the Finnish Genetic Study of Arrhythmic Events (Fingesture) study utilized a more extensive classification, including hypertensive, obesity-related and alcoholic CM, which have not been supported by the official statements. We will first discuss the CMs established in the 2007 ESC position statement and then proceed to review the other CMs used in the Fingesture study.

Dilated CM is the most common CM, defined by a dilated left ventricle or both ventricles without abnormal loading conditions or CAD (Elliott et al., 2008). An earlier study from Olmsted County, US reported a prevalence of 37 per 100,000, (Codd et al., 1989). This might be an underestimation, as left ventricular dysfunction is often asymptomatic (Devereux et al., 2001). The prevalence of dilated CM has been further estimated to be twice the prevalence of hypertrophic CM, approximately 400 in 100,000 (Hershberger et al., 2013). Dilated CM impairs systolic function and is often accompanied by heart failure and reduced ejection fraction (Chazov et al., 1980). Approximately one fourth of dilated CM cases are due to various genetic causes (Petretta et al., 2011). Other causes include viral infections, alcohol, prescribed and illicit drugs, and prolonged tachycardia (Braunwald, 2017). The symptoms of dilated CM are mostly caused by systolic dysfunction and include dyspnea, fatigue, edema, palpitations, syncope and SCA

(A. S. Manolis, 2017). Dilated CM is the most common indication for heart transplantation (Thekkudan et al., 2010).

Hypertrophic CM is characterized by left ventricular hypertrophy, often accompanied by left ventricular outflow obstruction, heart failure caused by diastolic dysfunction, and mitral regurgitation (Wigle et al., 1995). Thickening of the left ventricular wall is caused by myocyte hypertrophy and interstitial fibrosis (Shirani et al., 2000). Hypertrophic CM is generally classified as a genetic disease; however, perhaps due to the multitude of associated mutations, genetic foundation is identified in only 60–70% of the patients (Richard et al., 2003; Van Driest et al., 2005). Hypertrophic CM is often asymptomatic and relatively benign. A subset of patients develops a more progressive form, often accompanied by early diagnosis and symptoms similar to those of dilated CM (Maron et al., 1978, 1999). The prevalence of hypertrophic CM in Olmsted County was 20 per 100,000 (Codd et al., 1989). Another study of 4,111 young adults reported a prevalence of 170 per 100,000 (Maron et al., 1995). Patients with hypertrophic CM have a 3- to 4-fold higher mortality rate compared to the general population (Ho et al., 2018).

Restrictive CM is a rare form of CM characterized by severe diastolic dysfunction, with ventricular wall thickness and ejection fraction only mildly altered at maximum (Richardson et al., 1996). The causes of restrictive CM vary from genetic causes to toxic, inflammatory and infiltrative etiologies (Muchtar et al., 2017). Arrhythmogenic right ventricular CM is an inherited disease, characterized by fibrofatty replacement of the myocardium in the right ventricle. The prevalence of arrhythmogenic CM has been estimated at 20–50 per 100,000 (McKenna et al., 2017). Arrhythmogenic CM is a prevalent cause of SCD in the young (Tabib et al., 2003). The definition of unclassified CM varies, but according to the general consensus, it includes rarities such as left ventricular noncompaction, endocardiac fibroelastosis, and Takotsubo CM (Elliott et al., 2008; Maron et al., 2006).

Hypertensive CM is characterized by left ventricular hypertrophy and myocardial fibrosis induced by hypertension (Hookana et al., 2011). The term is often used interchangeably with hypertensive heart disease, which is the basis for our classification of hypertensive CM in the International Classification of Diseases, Tenth Revision (ICD-10). Hypertensive CM is essentially a response to the increased afterload caused by chronically elevated arterial pressure and peripheral vascular resistance (Mensah et al., 2002). In the Framingham study, the prevalence of left ventricular hypertrophy was 6% in the general population and 22% in those over 40 years (Haider et al., 1998; Kannel & Abbott, 1986). In the latter population,

left ventricular hypertrophy was associated with SCD with a 2.2 hazard ratio ($p = 0.008$). A more recent study from Thailand reported left ventricular hypertrophy in 6.6% of 638 adults (Viwatrangkul et al., 2021). Left ventricular hypertrophy seems to occur in around 27% of hypertension patients (Koren, 1991). Koren et al. (1991) reported two SCDs in 69 hypertension patients with left ventricular hypertrophy and zero SCDs in 184 hypertension patients without left ventricular hypertrophy during the 10-year study period. As CAD was included as a cause of death in these studies, the findings cannot be generalized to describe hypertensive CM patients. A recent study reported hypertensive heart disease as the cause of SCD in 75 (1.4 %) out of 5,239 autopsy-verified victims (Aung et al., 2022). Only two had an antemortem diagnosis of hypertensive heart disease, which underlines the importance of autopsy in recognizing hypertensive CM.

Obesity CM is characterized by hypertrophy in the left or both ventricles, increased heart weight and long-term obesity with no other identifiable cause of CM (Hookana et al., 2011). Excess weight increases blood volume, peripheral vascular resistance, preload and afterload, resulting in left ventricular hypertrophy (Ren et al., 2021; Vasan, 2003). Obesity often causes sleep apnea, which may result in pulmonary hypertension and right ventricular hypertrophy. Systemic inflammation, insulin resistance and atrial fibrillation frequently contribute to the dysfunction of the heart (Ren et al., 2021). The risk of SCD attributed to obesity CM is unknown.

Alcoholic CM is characterized by dilation of the left or both ventricles, normal or reduced ventricular wall thickness, impaired systolic function, long-term heavy alcohol consumption and lack of other diseases sufficient to explain the cardiac changes (Mirijello et al., 2017). Approximately 30–50% of nonischemic CM cases have been linked to alcohol abuse (Gardner & Mouton, 2015). Alcoholic CM is usually classified as secondary dilated CM, and alcoholic CM constitutes about 30–40% of dilated CM cases (Guzzo-Merello, 2014). An estimated consumption of 7–8 drinks per day for at least 5 years may lead to alcoholic CM, but not all chronic heavy drinkers develop the disease (Gardner & Mouton, 2015). Even severe alcoholic CM may be reversible with total abstinence (Guillo et al., 1997); without abstinence, cardiac mortality is substantially higher than in dilated CM (Fauchier, 2000). Alcoholic CM is a prevalent cause of SCD (Hookana et al., 2011; Vikhert et al., 1986). Guzzo-Merello et al. reported a 12% 1-year mortality rate in alcoholic CM patients (Guzzo-Merello et al., 2015). QT prolongation has been associated with SCD in alcoholics (Campbell et al., 1993). Cirrhotic CM, characterized by hepatic cirrhosis, subsequent hemodynamic changes and both systolic and diastolic

dysfunction, is sometimes viewed as a separate entity from alcoholic CM (Møller & Henriksen, 2002). Takotsubo CM, sometimes called broken heart syndrome, is a rare and reversible cause of left ventricular dysfunction. It typically occurs in postmenopausal women after sudden unexpected physical or emotional stress and may rarely cause arrhythmias and SCA (Akashi et al., 2008; Syed et al., 2011).

The mechanisms of arrhythmia in nonischemic CMs are thought to involve anatomical and functional reentry, triggered activity, and abnormal ventricular automaticity (B. A. Steinberg et al., 2017). These phenomena are enabled by structural alterations in the myocardium (ie. hypertrophy and fibrotic scarring), changes in action potential due to altered ionic currents, and an abnormal neurohormonal milieu caused by heart failure (B. A. Steinberg et al., 2017). Interestingly, myocardial hypertrophy was originally seen as a beneficial compensatory mechanism which increases cardiac output in response to the pressure overload caused by, eg., hypertension or valvular heart disease (Frey et al., 2004). Similar changes are seen in healthy athletes (Rawlins et al., 2009). Systolic dysfunction and heart failure were originally thought to result from insufficient hypertrophic compensation, but further studies have revealed that hypertrophy is rather a cause of heart failure (Vogt et al., 1993). Absence of ventricular hypertrophy seen in a subset of patients with severe aortic stenosis has also resulted in better preserved ejection fraction (Kupari et al., 2005). Further studies have shown that myocardial hypertrophy is usually a maladaptive phenomenon, as it impairs cardiac function and promotes ischemia and arrhythmogenesis (Frey & Olson, 2003).

Inherited ion channel disorders

LQTS is a congenital disorder characterized by prolonged ventricular repolarization and risk of lethal arrhythmia. It is the most common ion channel SCA-causing disorder, reaching a prevalence of about 100 in 100,000, out of which the penetrance of QT prolongation seems to be only about 20% (Priori et al., 1999; Schwartz et al., 2009). LQTS is typically diagnosed during childhood, adolescence or young adulthood (Moss et al., 1991). The majority of individuals remain asymptomatic throughout life. Symptoms typically appear after exercise, especially swimming in LQTS1, or acute arousal due to a sudden noise or a strong emotion, and they include syncope, nonfatal SCA, and SCD (Garson et al., 1993; Moss et al., 1991). Unlike in most other NIHDs, women seem to constitute about 60–70% of the patients (Locati et al., 1998; Moss et al., 1991). LQTS comprises two

different clinical phenotypes. The autosomal dominant form, or Romano-Ward syndrome, includes the types of LQTS which only affect the heart, such as LQTS1 and LQTS2. The Jervell and Lange-Nielsen syndrome, the rare autosomal recessive form, causes sensorineural deafness as well as arrhythmias and has a more malign prognosis (Grant, 2009). LQTS1 accounts for about half of all LQTS cases and is caused by mutations which disrupt the function of slow K^+ current during phase 3 (Napolitano et al., 2005; Ponte et al., 2009). LQTS2 is caused by mutations in hERG and is responsible for about 40% of LQTS cases (Napolitano et al., 2005; Ponte et al., 2009).

In addition to inherited channelopathies, acquired factors, typically medications, can also result in LQTS. Inhibition of hERG K^+ channel currents is the cause of QT prolongation in virtually all of these drugs (Roden, 2006). In this way, acquired LQTS mimics LQTS2. According to the "multiple hit hypothesis", many factors often contribute to the effect, both in congenital and acquired LQTS (Ponte et al., 2009). Indeed it seems that most individuals with drug-induced torsades de pointes also have other risk factors, such as female sex, seniority, polypharmacy, hypokalemia, hypomagnesemia, heart failure or existing proarrhythmic changes in ECG (Girardin et al., 2013; Kallergis et al., 2012; Trinkley et al., 2013). Despite the assessment of risk factors, the extent of QT prolongation caused by a medication seems rather unpredictable, or patient-specific. Multiple ion currents are responsible for regulating repolarization, and thus the effect of a drug on one ion channel might not cause any clinical effects but only result in more vulnerability to further QT prolonging factors, or "reduced repolarization reserve" (Roden, 2006). With the same mechanism, initiation of a QT-prolonging drug might reveal an underlying QT-prolonging ion channel mutation or polymorphism (Modell & Lehmann, 2006; Ponte et al., 2009). In some cases of acquired LQTS, eliminating risk factors does not reverse the QT prolongation, which led to an early theory that genetic factors might indeed play a role in acquired LQTS (Moss & Schwartz, 1982). Decades later, as many as a third of acquired LQTS patients have been demonstrated to carry LQTS mutations (Itoh et al., 2016).

Short QT syndrome is an extremely rare inherited channelopathy which was first identified only two decades ago (Gussak et al., 2000). A total of nine mutations in three genes have been identified to cause short QT syndrome (Campuzano et al., 2019). Individuals with short QT syndrome may experience palpitations, syncope, atrial fibrillation, SCA and SCD (Bjerregaard, 2018; Giustetto et al., 2006). Short QT interval (< 400 ms) has been associated with SCD, but the findings are not

consistent (Algra et al., 1993). In a Finnish cohort study of 10,882 middle-aged people, 0.4% had a corrected QT interval < 340 ms, but no lethal arrhythmias were observed in this population (Anttonen et al., 2007). Thus, as a short QT interval is rather common in the general population, it should not be automatically considered pathologic. Nevertheless, according to 2015 European Society of Cardiology Guidelines, a corrected QT interval ≤ 340 ms ought to be interpreted as short QT syndrome, whereas a corrected QT interval of ≤ 360 ms should be considered as short QT syndrome in case of a confirmed short QT syndrome mutation, a family history of short QT syndrome or SCD before the age of 40 years, or if the individual has survived a VF/VT episode without detected heart disease (Priori et al., 2015).

Brugada syndrome is an autosomal dominant inherited channelopathy. The typical ECG pattern includes a pseudo-right bundle branch block and an elevated ST segment, which may not be a predictor of SCA in asymptomatic individuals (Junttila et al., 2004). The prevalence of the Brugada syndrome has been estimated at 1–50 per 100,000, although the Brugada pattern is much more common (Holst et al., 2012; Patel et al., 2009; Risgaard et al., 2013). In a Finnish study, the Brugada pattern was found in 0.6% of 3,021 healthy individuals, but no cases of Brugada syndrome were detected (Junttila et al., 2004). Brugada syndrome is typically diagnosed during adulthood and is more common in men (Matsuo et al., 2001). The genetic basis of Brugada syndrome is still unclear, as the recognized mutations are only responsible for one third of Brugada syndrome cases (Al-Khatib et al., 2018).

Catecholaminergic polymorphic VT is a rare genetic channelopathy, which consists of the more common autosomal dominant form and an autosomal recessive form. Mutations in one gene have been identified for each form (Priori et al., 2021). The mechanism of action is induced Ca^{2+} release from the sarcoplasmic reticulum in both types. The prevalence of catecholaminergic polymorphic VT seems to be around 10 in 100,000 (Priori et al., 2013). As in other channelopathies, some patients remain asymptomatic, while others develop palpitations, syncope, SCA and SCD due to polymorphic VT. The resting ECG is typically normal, as the symptoms and ECG changes often emerge only during emotional stress or physical exercise (Priori et al., 2002). Catecholaminergic polymorphic VT is often diagnosed during childhood (Singh et al., 2019).

Other types of nonischemic heart disease

Valvular heart disease is one of the most common types of NIHD, with a prevalence of 2,500 per 100,000 in the United States (Nkomo et al., 2006). Degenerative

etiologies are nowadays most prevalent in Western countries, whereas rheumatic heart disease is still the most common cause worldwide and in developing countries (James et al., 2018; Tibazarwa et al., 2008; Watkins et al., 2017). Men and women seem to have a similar prevalence which increases sharply after 65 years (Nkomo et al., 2006; Yadgir et al., 2020). Valvular defects can be divided into regurgitation and stenosis. Regurgitation is the backward flow of blood through a valve which does not close properly. Stenosis, on the other hand, reduces the onward blood flow by preventing the valve from opening fully. Mild-to-moderate valvular disease is often asymptomatic, but especially more severe cases may cause palpitations, chest pain, dyspnea, fatigue, syncope, hemodynamic changes, heart failure and even death (Yadgir et al., 2020).

Mitral valve regurgitation is the most common valvular disease (Chehab et al., 2020). Primary mitral valve regurgitation is a disorder of the valve itself, whereas the secondary form is caused by abnormalities of the left ventricle. Degenerative mitral valve prolapse is the most common cause of primary mitral valve regurgitation in Western countries (El Sabbagh et al., 2018). A meta-analysis reported a prevalence of mitral valve prolapse at 1,200 per 100,000 individuals (Nalliah et al., 2019). Secondary mitral regurgitation is often due to left ventricular dysfunction related to previous myocardial ischemia or dilated CM (Chehab et al., 2020). Mitral regurgitation after myocardial infarction is associated with increased mortality (Lamas et al., 1997). Mitral stenosis is predominantly of rheumatic etiology and is rare nowadays in Western societies (Horstkotte et al., 1991).

Aortic valve stenosis is the second most common type of valvular disease. In Western countries, it is predominantly caused by aortic calcification of a trileaflet valve, or a congenital bicuspid valve (Thaden et al., 2014). A bicuspic aortic valve seems to comprise almost half of all stenotic valves removed by aortic valve replacement, even though the prevalence of a bicuspid valve is only 1.4% in the United States (Go et al., 2013; Roberts & Ko, 2005). According to a Finnish study, aortic sclerosis is seen in more than half and aortic stenosis in more than a third of individuals over 80 years (Lindroos et al., 1993). One meta-analysis reported a 12.4% prevalence of aortic stenosis in individuals over 75 years (Osnabrugge et al., 2013). Aortic stenosis is relatively uncommon in individuals < 60 years, and the prevalence increases rapidly with age (Eveborn et al., 2013). Other risk factors include male gender, hypertension, hypercholesterolemia and smoking (Palta et al., 2000; Ramaraj & Sorrell, 2008). Aortic regurgitation is less common, with a reported prevalence of 4.9% in the Western societies (Maurer, 2006). Aortic root dilatation, a congenital bicuspid valve and other valve malformations may lead to

the chronic disease, whereas acute aortic regurgitation is often caused by endocarditis, aortic dissection or trauma (Maurer, 2006).

Myocarditis is an inflammatory disease of the cardiac muscle. The golden standard for diagnosis is endomyocardial biopsy, which is used infrequently (Caforio et al., 2013). Myocarditis can be acute, subacute or chronic. The global annual incidence of myocarditis was estimated to be 40 per 100,000 individuals in 2017 (James et al., 2018). The etiology of myocarditis is partly unknown. Autoimmune mechanisms have been indicated in the development, and some patients have a familial predisposition to myocarditis (Caforio et al., 2013). Viral infection is a common trigger, but medications and vaccinations can also precede myocarditis (Ben M'rad et al., 2009; Bowles et al., 2003; Engler et al., 2015). Some cases are linked to autoimmune diseases, such as systemic lupus erythematosus (Wijetunga & Rockson, 2002). Myocarditis, especially the acute form, can cause conduction abnormalities, as well as tachyarrhythmias and SCA. Persistent myocarditis can cause cardiac dysfunction and progress to dilated CM (Bowles et al., 2003; Kühl et al., 2005). Endocarditis is an inflammatory disease of the endocardium, i.e., the inner layer of the heart including the valves. Endocarditis is usually not considered a SCA-inducing disease. However, in a study of 6,000 autopsy-verified victims of SCD (mean age 36±20 years), endocarditis was found to be the cause of death in 30 (0.5%) cases (S. T. E. Cooper et al., 2021).

Wolff-Parkinson-White (WPW) syndrome is a conduction disorder characterized by ECG changes and risk of lethal tachyarrhythmias. An accessory pathway bypasses the atrioventricular node, leading to preexcitation and the typical ECG pattern, which includes a shortened PQ interval and a widened QRS complex due to a delta wave (Wolff et al., 2006). WPW syndrome is familial at least in part, and the congenital form might be associated with a higher risk of SCD (Gollob et al., 2001; Vidaillet et al., 1987). The prevalence of the WPW pattern is estimated at 100–250 per 100,000 individuals (Kobza et al., 2011; Krahn et al., 1992). The prevalence of WPW syndrome is much lower: in a longitudinal study including 187 individuals with WPW pattern without a history of arrhythmia, only 15% experienced arrhythmias during the 22-year study period, and the annual rate of WPW-associated SCD was 0.02% (Fitzsimmons et al., 2001).

Coronary artery anomalies are a group of congenital disorders present in about 1% of the general population (Kardos et al., 1997). A coronary artery may have an abnormal origin, shape, course or termination, or an artery may be totally absent. Although rarely fatal in the general population, anomalous coronary arteries are a notable cause of ischemia and SCD in young athletes (Greet et al., 2012; Kardos et

al., 1997; Maron et al., 2007). Cardiac amyloidosis is a heterogeneous group of rare diseases in which protein deposits infiltrate the myocardium. The prognosis is poor, as the median survival time from diagnosis is less than a year (Tahir et al., 2019). Most deaths are due to heart failure (D'Errico et al., 2020). SCD without heart failure, often with PEA as the initial rhythm, has been observed in about 20% of cardiac amyloidosis patients (D'Errico et al., 2020). Cardiac sarcoidosis is a rare inflammatory disorder in which clusters of white blood cells form granulomas in the myocardium. Although not usually lethal, sarcoidosis has been associated with an increased risk of heart failure, ventricular arrhythmias and SCD (Yafasova et al., 2020).

2.4 Risk factors for sudden cardiac arrest

2.4.1 Role of underlying heart disease

Following the invention of medical and interventional therapies for stable CAD as well as acute coronary syndrome, CAD mortality has steadily declined since the 1970s (Fox et al., 2004; Mensah et al., 2017), occurring in about 1.2–2.4% CAD patients annually. Patients with non-obstructive coronary plaques have a 0.6% annual mortality rate, whereas a 3.8% one-year mortality rate has been reported in high-risk patients (Montalescot et al., 2013; Steg et al., 2007). The annual SCD rate has been reported at 0.79% in postmenopausal women, with multiple prior myocardial infarctions, congestive heart failure, atrial fibrillation and glomerular filtration rate < 40 increasing the risk (Deo et al., 2011). Ventricular arrhythmias are more common in men with CAD compared to women (R. Lampert et al., 2004). SCA with VF has been reported in about 5% of acute myocardial infarctions, and VF drastically increases the risk of death during myocardial infarction (44% vs. 5%) (Thompson et al., 2000). The factors associated with VF were a pathological Q wave in ECG, administration of lidocaine or other antiarrhythmic agents, and thrombolysis, whereas age, sex and type of coronary interventional procedure had no significant effect on the occurrence of VF. Annual SCD rates of 1–4% have been reported after myocardial infarction (S. Lampert et al., 1988; Mäkikallio et al., 2005). Henkel et al. reported ventricular arrhythmias in 6.8% of CAD patients after myocardial infarction during 1994–1998 (Henkel et al., 2006). Myocardial infarction often results in chronic heart failure, which increases the risk of subsequent SCD especially during the first 30 days after myocardial infarction

(Solomon et al., 2005). Heart failure with reduced ejection fraction has also been reported to increase mortality in CAD patients with a history of VF/VT (De Sutter et al., 2000).

The risk of SCA in NIHD varies greatly according to the type of NIHD. According to a meta-analysis of 11,451 patients with dilated CM, the annual rate of sustained ventricular arrhythmias is 4.5% (Sammani et al., 2020). Another meta-analysis demonstrated a 3-year arrhythmic event rate of 19% in 6,088 dilated CM patients (Goldberger et al., 2014). Similar results have been released from trials examining the benefit of implantable cardioverter-defibrillators: in a study of 458 dilated CM patients, 6% experienced SCD in the standard therapy group and 1% in the cardioverter-defibrillator group (Kadish et al., 2004). Detection of VT episodes during ambulatory monitoring has been associated with subsequent SCA in dilated CM patients (Holmes et al., 1985; Meinertz et al., 1984), although the findings are not consistent (Milner et al., 1988). Hypertrophic CM is also associated with an increased risk of SCD (Lorenzini et al., 2020). Non-sustained VT, an arrhythmia associated with subsequent SCD, has been detected in almost a third of hypertrophic CM patients during 24–72-hour ambulatory monitoring (Adabag et al., 2005; McKenna et al., 1981). Possessing multiple risk factors, such as syncope, non-sustained VT, family history of SCD and ventricular wall thickness, has been shown to significantly increase the risk of SCA (RR 5.6, $p = 0.002$) (Elliott et al., 2000). A longitudinal study of 428 hypertrophic CM patients ≥ 60 years reported a 0.2% annual risk of ventricular arrhythmias or SCA (Maron et al., 2013), and higher incidences have also been observed (Lorenzini et al., 2020; Pujades-Rodriguez et al., 2018). A meta-analysis reported annual ventricular arrhythmia or SCA rates at 0.6–2% in hypertrophic CM patients (Elliott et al., 2006). A cumulative lifetime incidence of ventricular arrhythmias has been reported to be 32% in hypertrophic CM patients diagnosed before 40 years of age (Ho et al., 2018). As patient age at diagnosis increases, the risk of SCD actually decreases, as achieving older age in a progressive illness indicates a more favorable prognosis (Maron et al., 2013). One study reported a 3.8-fold increased risk of SCA or death in children with restrictive CM compared to hypertrophic CM (Maskatia et al., 2012). In a recent study of 864 patients with arrhythmogenic CM, life-threatening ventricular arrhythmia was observed in 11% and SCA in 1.7% of the participants (median follow-up 5.75 years) (Cadrin-Tourigny et al., 2021). Cadrin-Tourigny et al. have also reported a 5.6% annual event rate (sustained VT, appropriate cardioverter-defibrillator shock, SCA or SCD) in arrhythmogenic CM patients (Cadrin-Tourigny et al., 2019).

Estimating the risk of SCA in inherited ion channel disorders is challenging, as many studies include all individuals with the associated ECG pattern without genetic verification or fulfilling other diagnostic criteria (Antzelevitch et al., 2005), which might cause overestimation of the prevalence of the disease and underestimation of the related incidence of SCA. The annual SCA rate among individuals with LQTS mutations has been reported to be 0.3–1% (Priori et al., 2003). Rohatgi et al. observed a 1.2% annual arrhythmic event rate in patients with LQTS syndrome (Rohatgi et al., 2017). A 1.6% annual event rate has been reported in patients with Brugada syndrome (Probst et al., 2010). Hayashi et al. (2009) observed a 12% 4-year cardiac event rate (syncope, SCA or SCD) in 101 catecholaminergic polymorphic VT patients (Hayashi et al., 2009), and a 5.6% annual rate of recurrent syncope, SCA or SCD has also been reported (Sy et al., 2011).

The risk of SCA in valvular disease varies greatly according to the type and severity of the condition. A meta-analysis reported an annual SCD incidence of 0.14% in mitral valve prolapse patients (Nalliah et al., 2019), but incidences as high as 0.4% have been observed previously (Nishimura et al., 1985). Severe regurgitation, thickened or flail leaflets, concurrent atrial fibrillation or CAD, female sex and older age indicate a more malign prognosis and a higher risk of stroke and SCD (Düren et al., 1988; Grigioni et al., 1999; Han et al., 2018; Pérez-Gómez et al., 2006). The mechanism of SCD in mitral valve regurgitation involves repolarization abnormalities, alterations in the mitral valve structure, and triggered activity caused by hypertrophy and fibrosis in the fascicular tissue and papillary muscles (Spartalis et al., 2017). SCD may in some cases be the first symptom of aortic stenosis: Minners et al. reported a 0.4% annual incidence of SCD in asymptomatic patients (Minners et al., 2020; Pellikka et al., 2005). Severe aortic stenosis is the strongest predictor of an adverse clinical outcome, the risk of which aortic valve replacement effectively decreases (Kang et al., 2020; Vahanian & Otto, 2010). The hypotheses for the mechanism of SCD in aortic stenosis include bradycardia due to an abnormal left ventricular baroreceptor reflex (Bezold-Jarisch reflex), predisposition to arrhythmias due to left ventricular hypertrophy and atrioventricular conduction disturbances caused by valvular calcification (Friedman et al., 1978; Johnson, 1971). The risk of SCA related to myocarditis is unknown, but myocarditis seems to constitute up to 40% of SCDs in young people and about 5% of all SCD cases (Basso et al., 2001; Hookana et al., 2011).

Given that the various types of NIHD have quite different pathogeneses and risks, comparing ischemic and nonischemic SCA is challenging. Some studies have

compared implantable cardioverter-defibrillator therapy in ischemic and nonischemic, mostly dilated, CMs. Ischemic and nonischemic CMs seem to have similar rates of cardiovascular mortality and SCD (Rusnak et al., 2020; Ursaru et al., 2021; Verhagen et al., 2014). The rate of ventricular arrhythmia also seem to be similar, although Rusnak et al. reported more frequent arrhythmias in nonischemic CM (33% versus 14%, hazard ratio 1.8, p = 0.025) (Rusnak et al., 2020; Ursaru et al., 2021; Verhagen et al., 2014). NIHD seems to be a more prevalent cause of SCD among women compared to men (Haukilahti et al., 2019). The annual rates of sustained ventricular arrhythmia or SCA in different types of heart disease are illustrated in Table 1.

Table 1. Prevalence and risk of sudden cardiac death in different types of heart disease.

Type of heart disease	Prevalence per 100,000	Annual rate of sustained ventricular arrhythmias or SCA	References
General population	100,000	0.19%	Khurshid et al. 2018
CAD	6,400	1–4% for post-MI SCD	Go et al. 2013; Lampert et al. 1988; Mäkikallio et al. 2005
Mitral regurgitation	1,200	0.14–0.4%	Nalliah et al. 2019; Nishimura et al. 1985
Aortic stenosis	1,200 (> 75 years)	0.4% in asymptomatic patients	Osnabrugge et al. 2013; Minners et al. 2004
Dilated CM	400	4.5%	Hershberger et al. 2013; Sammani et al. 2020
Hypertrophic CM	200	1.0%	Maron et al. 1995; Hershberger et al. 2013; Elliott et al. 2006
Arrhythmogenic CM	20–50	5.6%	McKenna et al. 2017; Cadrin-Tourigny et al. 2019
Myocarditis	50	Unknown	James et al. 2018
Long QT syndrome mutation	100	1.2%	Priori et al. 1999; Schwartz et al. 2009; Rohatgi et al. 2017
Brugada syndrome	1-50	1.6%	Holst et al. 2012; Risgaard et al. 2013; Probst et al. 2010
Cathecoliaminergic polymorphic VT	10	5.6%	Priori et al. 2013; Sy et al. 2011

CAD = coronary artery disease, CM = cardiomyopathy, ECG = electrocardiography, MI = myocardial infarction, SCA = sudden cardiac arrest, SCD = sudden cardiac death

2.4.2 Comorbidity

Other cardiovascular diseases, such as hypertension and diabetes, often precede CAD and NIHD. In addition to them being long known as risk factors for CAD,

the relationship of comorbidities and SCD has also been extensively studied. Hypertension, which affects one third of adults around the globe, doubles the risk of SCD (Mills et al., 2020; Pan et al., 2020). According to a meta-analysis, antihypertensive pharmacotherapy reduces the risk of both fatal and non-fatal myocardial infarction, but not the risk of SCD (Taverny et al., 2015). The relationship of antihypertensive medication and NIHD as the cause of death was not examined separately, and thus it remains unknown whether NIHD represented the part of the study population that did not benefit from the medication. About 6% of the global population suffer from type 1 or type 2 diabetes, which, according to another meta-analysis, likewise doubles the risk of SCD (Aune et al., 2018b; James et al., 2018). Heart failure due to ischemic or NIHD significantly increases the risk of SCD (Pimentel et al., 2017). Atrial fibrillation often manifests after myocardial infarction or in nonischemic CMs, and it increases the risk of ischemic stroke, heart failure and myocardial ischemia (Ducas & Ariyarajah, 2013; Patten et al., 2018; Wijesurendra & Casadei, 2019). According to a meta-analysis, atrial fibrillation increases the risk of SCD in the general population as well as in individuals with ischemic or NIHD (Rattanawong et al., 2018). Chronic kidney disease, especially end-stage renal disease, causes hemodynamic stress and metabolic changes which may lead to atherosclerosis and SCD (Di Lullo et al., 2016). Left ventricular hypertrophy is common in patients with chronic kidney disease, and the combination is also known as uremic CM. Obstructive sleep apnea affects around 10–35% of the global adult population and has been established as a risk factor for cardiovascular disease and myocardial ischemia but not for SCD, perhaps due to the lack of sufficient epidemiological studies (Blackwell et al., 2019). Many infections, such as human immunodeficiency virus and coronavirus disease 2019, have also been suspected to associate with SCD (Baldi et al., 2020; Tseng et al., 2021).

Mental disorders affect 13% of the global population every year, as 3% of the population suffer from depression, 4% from anxiety disorders and 0.3% from schizophrenia (James et al., 2018). These psychiatric comorbidities have been recognized to associate with cardiovascular disease and SCD. The association appears multifactorial, with lifestyle factors, symptom progression and medication all contributing to the effect. Many cardiovascular risk factors, such as smoking, weight gain, dyslipidemia, hypertension and diabetes, are more prevalent in mental health patients compared to the general population (Li et al., 2018). According to a meta-analysis, depression increases the risk of cardiac events by 80% (Nicholson et al., 2006). Depressive symptoms have also been reported to individually increase

the risk of SCD among an elderly population (Luukinen et al., 2003). In patients with schizophrenia, aggressive symptoms have been suggested as a risk factor for SCD (Hou et al., 2015). Symptom and disease progression might indeed play a role in the risk of SCD related to psychiatric disorders, as despite the cardiovascular risk attributed to psychotropic pharmacotherapy, untreated schizophrenia causes a greater increase in all-cause and cardiovascular mortality compared to schizophrenia treated with antipsychotics (Taipale et al., 2020). Depression is especially common among patients with CAD. About 40% of these individuals suffer from depression (Dickens, 2015), and depression after acute myocardial infarction increases the risk of a successive cardiac event with an OR of 1.95 (Van Melle et al., 2004). Schizophrenia has been associated with Brugada pattern in ECG, but the association of the pattern with SCD in this population has not been studied (Blom et al., 2014).

2.4.3 Role of medication

Psychotropic medication

Psychotropic medication is the second most prescribed type of medicine in Finland, the first being cardiovascular medication (Finnish Medicines Agency & Social Insurance Institution, 2018). Psychotropic medications include benzodiazepines, antidepressants and antipsychotics. Benzodiazepines, such as lorazepam or diazepam, are mainly used for anxiety disorders, epileptic seizures, spasticity etc. Antidepressants include tricyclic antidepressants such as amitriptyline and doxepin, selective serotonin reuptake inhibitors such as citalopram and sertraline, monoamine oxidase inhibitors such as moclobemide, and new antidepressants such as venlafaxine and mirtazapine. Antipsychotics are primarily used for schizophrenia and other psychotic disorders, as well as bipolar disorder and behavioral symptoms of dementia. Antipsychotics include lithium, first-generation antipsychotics such as haloperidol, chlorpromazine and thioridazine, and second-generation or atypical antipsychotics such as olanzapine, clozapine, aripiprazole, quetiapine and risperidone. Many of these agents are nowadays used for insomnia and pain, often in smaller doses compared to the original indication. Other hypnotics and sedatives, such as zopiclone and melatonin, or psychostimulants such as dexamfetamine, are not counted among psychotropics in this thesis. In 2018, 7.5% of the Finnish population were estimated to use antidepressants and 2.2%

antipsychotics (Finnish Medicines Agency & Social Insurance Institution, 2018). According to previous studies, the prevalence of antidepressant use was about 8.7% in the Australian population and 4.6% in Taiwan, and antipsychotic use was 1.0% in Australia and 0.5–1.3% in Europe (Raschi et al., 2013; Stephenson et al., 2013; C.-S. Wu et al., 2012). Most of these estimates were originally presented as defined daily dose/1,000 inhabitants/day.

Psychotropic medications, especially antipsychotics, have been associated with an increased risk of SCA (Ray et al., 2001; C.-S. Wu et al., 2015). The risk has been mainly attributed to the QT-interval-prolonging effect of most antidepressants and antipsychotics (Sicouri & Antzelevitch, 2018). Selective serotonin reuptake inhibitors and tricyclic antidepressants, as well as newer antidepressants, e.g. mirtazapine, have been reported to prolong the QT interval (Gurkan et al., 2019; T. A. Manolis et al., 2019). Tricyclic medication may widen the QRS complex and thus induce reentry and ventricular arrhythmias (Frassati et al., 2004). In patients with a bundle branch block, tricyclic antidepressants may also cause a second- or third-degree atrioventricular block and eventually, asystole or other fatal arrhythmias (Roose et al., 1987). Many antidepressants and antipsychotics can cause tachycardia or bradycardia. Although not usually dangerous, bradycardia can be an adjunct to a bundle branch block or a complete heart block, which might provoke asystole or rapid ventricular arrhythmia (T. A. Manolis et al., 2019). Some psychotropics cause postural hypotension and syncope, and enhanced autonomic reflexes often seen in psychiatric patients can also trigger a brief collapse (T. A. Manolis et al., 2019). In these cases, it is crucial to differentiate between benign syncope and malignant ventricular arrhythmia as the cause of collapse. Psychotropic pharmacotherapy also increases the risk of SCA due to metabolic factors. Antidepressants and antipsychotics can cause weight gain and have negative effects on glucose and lipid metabolism, and new antidepressants may increase blood pressure (T. A. Manolis et al., 2019; C.-S. Wu et al., 2014).

Out of antidepressants, selective serotonin reuptake inhibitors, and especially sertraline, seems to be the safest choice for patients with cardiovascular disease or other risk factors for arrhythmias (Beach et al., 2018). Atypical antipsychotics were at first considered significantly safer than first-generation antipsychotics, but both categories include agents with substantial QT prolongation and a dose-dependent risk of SCA (A. S. Manolis, 2017; Ray et al., 2009; C.-S. Wu et al., 2015). Aripiprazole appears the safest atypical antipsychotic for the heart (Beach et al., 2018). Benzodiazepines have not been reported to increase the risk of SCA and

might even be cardioprotective on some occasions (Kovacs & Arora, 2008; A. S. Manolis, 2017; C. K. Wu et al., 2014).

Few studies have assessed the risk of SCA due to a specific heart disease in users of psychotropic medication. In 1992, before atypical antipsychotics were widely used, psychotropic pharmacotherapy was reported to increase the risk of fatal myocardial infarction in young women (Thorogood et al., 1992). Use of antidepressants and antipsychotics has also been associated with SCD during an acute coronary event (Honkola et al., 2012). Studies concerning the risk of SCA due psychotropic use in patients with NIHD are especially scarce. Clozapine and some other atypical antipsychotics can occasionally cause myocarditis, which may lead to CM, heart failure and death if not timely reverted (Ronaldson et al., 2015). Two case reports suggested that risperidone or haloperidol might induce SCA in patients with hypertrophic or other CM (Marti, 2005; Remijnse et al., 2002). Several psychotropic drugs, such as amitriptyline and lithium, have been recorded to induce a Brugada pattern in ECG; however, most of these cases have been due to overdose (Konigstein et al., 2016; Rouleau et al., 2001).

Other QT-prolonging medication

Other medications which can prolong the QT interval mostly comprise antiarrhythmic medications, antihistamines, antimicrobial drugs and antiepileptic drugs (Yap & Camm, 2003). All antiarrhythmic drugs seem to have proarrhythmic properties. Class Ia antiarrhythmic drugs, such as quinidine and disopyramide, as well as class III antiarrhythmics, such as amiodarone and sotalol, have been demonstrated to induce torsades de pointes in about 1–8% of users (Yang et al., 2002). Unlike most other QT-prolonging drugs, class Ic antiarrhythmic medications, such as flecainide, block the inward Na^+ flow during phase 0 and thus prolong the QRS and QT intervals (Yap & Camm, 2003). Prenylamine, bepridil and terodiline are Ca^{2+} channel blockers which have been withdrawn from the market because of their QT-prolonging and arrhythmia-inducing effects (Yap & Camm, 2003). Newer Ca^{2+} channel blockers and angiotensin II receptor antagonists do not seem to have QT-lengthening effects (Porthan et al., 2009). Diuretics, such as furosemide and hydrochlorothiazide, can cause hypokalemia and might thus prolong the QT interval; however, this association has only been detected in animal studies (Hanton et al., 2007) and with a small effect (+3 ms) in patients with chronic kidney disease (Snitker et al., 2017). Beta blockers seem to have bidirectional effects on the QT

interval, as bisoprolol has been reported to shorten and sotalol to lengthen it (McKibbin et al., 1984; C. Steinberg et al., 2016).

Macrolide antibiotics such as erythromycin and azithromycin, fluoroquinolone antibiotics such as ciprofloxacin and levofloxacin, antifungals such as fluconazole, and some antimalarial drugs can prolong the QT interval (Ray et al., 2004; Tsikouris et al., 2006; J. Wang et al., 2016). Opioids, especially methadone, have also been reported to prolong the QT interval (Titus-Lay et al., 2021). Two second-generation antihistamines, astemizole and terfenadine, have been withdrawn from the market because of arrhythmia case reports; however, other antihistamines have not been reported to pose similar risks (Olasińska-Wiśniewska et al., 2014). Cisapride, a gastroprokinetic agent, has been associated with torsades de pointes and thus discontinued in multiple countries including Finland and the United States (Wysowski et al., 2001).

Other medication

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used pain medications which have been demonstrated to increase the risk of myocardial infarction and ischemic SCA, especially in patients with existing CAD (Anderson et al., 2013; Sondergaard et al., 2017). Patients with unstable angina pectoris or recent myocardial infarction are at particular risk for cardiovascular complications associated with NSAID use (Antman et al., 2007). The risk of myocardial infarction during NSAID use has also been demonstrated in the general population (Helin-Salmivaara et al., 2006). Cyclooxygenase-2-selective and non-selective NSAIDs seem to pose a similar effect, with the exception of naproxen, which might be slightly safer for the heart compared to the other agents (Bhala et al., 2013; Fosbøl et al., 2010; Sondergaard et al., 2017). The mechanism of the association is thought to be the inhibition of cyclooxygenase-2, which leads to reduced prostacyclin production and increased production of the potentially prothrombotic platelet thromboxane-2 (Caughey et al., 2001). This chain of events may lead to endothelial injury and myocardial infarction (Cheng et al., 2002). NSAIDs also block the effects of acetylsalicylic acid, which is technically a NSAID but more commonly used as a cardioprotective antithrombotic agent (Anderson et al., 2013).

Anabolic-androgenic steroids are illicitly used for enhancing performance and physical appearance, and as cardiotoxic agents they can cause left ventricular dysfunction and hypertrophy, and possibly predispose an individual to SCA (Climstein et al., 2003; H.M. Nascimento & Medei, 2011; Torrisi et al., 2020).

Digoxin, a positive inotropic agent used in atrial fibrillation, increases intracellular Ca^{2+} levels, shortens the action potential and QT interval, and decelerates atrioventricular conduction. All of these changes can lead to arrhythmias, and digoxin has been associated with SCD in the literature (Eisen et al., 2017). Many cancer chemotherapy agents, such as trastuzumab and anthracyclines, are cardiotoxic and can in some cases result in CM, myocarditis, or possibly even SCD (Eiger et al., 2020; Romond et al., 2012). Combined estrogen and progestin as postmenopausal hormone replacement and thiazolidinediones used for diabetes might increase the risk of cardiovascular events, but they have not been directly linked to SCA (Lago et al., 2007; Writing Group for the Women's Health Initiative Investigators, 2002; A. H. Wu, 2008). Estrogen is a cardioprotective agent which is thought to cause the observed smaller risk of cardiovascular disease and mortality in premenopausal women compared to postmenopausal women (Moolman, 2006). Postmenopausal estrogen therapy has been reported to decrease the risk of SCD (Sourander et al., 1998). Some drugs, including the withdrawn weight loss medication fenfluramine and the migraine medication ergotamine, have been reported to cause drug-induced valvular disease, and an earlier case report described myocardial ischemia after administration of ergotamine tartrate (A. H. Wu, 2008).

2.4.4 Substance abuse

Alcohol abuse

Chronic heavy alcohol usage has long been acknowledged as a risk factor for SCD (Ettinger et al., 1978; Wannamethee & Shaper, 1992). Light-to-moderate drinking has been associated with a lower risk of ventricular fibrosis, CAD, myocardial infarction, heart failure and even SCA (Albert et al., 1999; H. A. Cooper et al., 2000; Klatsky et al., 2005; Siscovick et al., 1986; Voskoboinik et al., 2019). It has been suggested, however, that the beneficial effects of light drinking might have been overestimated, as due to selection biases, some results may favor light drinkers compared to non-drinkers (Naimi et al., 2017; Sutanto et al., 2020). The mechanism of alcohol-induced SCD is not fully understood. Acute ethanol intake is known to temporarily reduce left ventricular function, induce platelet aggregation, decelerate cardiac conduction and promote reentrant arrhythmias, resulting in an increased risk of atrial fibrillation, myocardial infarction, stroke and SCD (Aung et al., 2022;

Friedman, 1984; Hillbom et al., 1985; Mostofsky et al., 2016; Sutanto et al., 2020). Even small amounts, such as one or two standard drinks, may temporarily predispose an individual to cardiovascular events (Mostofsky et al., 2016). Chronic heavy drinking increases blood pressure and cortisol levels, impairs ventricular function and may lead to alcoholic CM (Gardner & Mouton, 2015; Sutanto et al., 2020). Binge drinking has also been associated with ventricular arrhythmias and increased mortality (Ettinger et al., 1978; Mukamal et al., 2005). In a study based on the Fingesture population, 38% of 1,691 autopsied victims of ischemic SCD had alcohol in blood (Perkiömäki et al., 2016). Chronic heavy alcohol consumption is especially risky in patients with CAD (Mukamal et al., 2005; Wannamethee & Shaper, 1992); the risk of SCD attributed to alcohol in NIHD is not as well known.

Illicit drugs

A history of illicit drug use is common in young SCD victims (Morentin & Callado, 2019). Cocaine is perhaps the best known abused substance with cardiovascular effects, as it may cause myocardial ischemia (sometimes through vasospasm), cocaine-related CM, stroke and SCD due to its adrenergic, vasoconstrictive and platelet aggregating features (Felker et al., 2000; Heesch et al., 2000; Lucena et al., 2010; Mittleman et al., 1999). Cocaine may affect cardiac conduction and result in QT prolongation or Brugada-type ECG pattern (Fischbach, 2017). Methamphetamine has similarly been reported to prolong the QT interval and to increase the risk of SCD (Haning & Goebert, 2007; Huang et al., 2016). Persistent use may lead to methamphetamine-associated CM, heart failure, stroke and vasospastic myocardial infarction (Schürer et al., 2017). 3,4-Methylenedioxymethamphetamine, also known as MDMA or ecstasy, has been suspected of causing valvular heart disease (Droogmans et al., 2007). Although cannabis is by far the most commonly used illegal drug in Finland, intoxications aside, it rarely causes serious cardiovascular effects (Casier et al., 2014; Kauhanen & Tiihonen, 2017).

2.4.5 Lifestyle and other risk factors

Male gender is an established risk factor of SCA, as men have a 1.5–3 times the SCA incidence of women across all age groups (Haukilahti et al., 2019; Herlitz et al., 2007; Winkel et al., 2017). Increasing age is a risk factor for SCA (Abildstrom, 2002; Chugh et al., 2004; Schatzkin et al., 1984). A family history of SCA has been

demonstrated to increase the risk with a RR of 1.5–1.8, and the association was independent of known SCA risk factors (Friedlander et al., 1998; Jouven et al., 1999). The extent of genetic versus environmental factors affecting the familial clustering of SCA is still unclear. A higher incidence of SCA in areas of low compared to high socioeconomic status has also been reported (Reinier et al., 2006). Obesity is a risk factor for SCA: a 5-unit increase in body mass index has been demonstrated to increase the risk of SCD with a RR of 1.16 (Aune et al., 2018a). The relationship of obesity and mortality is, however, quite complex. Termed "obesity paradox", an observation has arisen that a positive association exists between obesity and improved survival in patients with existing cardiovascular disease, for example after percutaneous coronary intervention (Bundhun et al., 2015) and in chronic heart failure (Sharma et al., 2015). The conflicting results might be partly explained by differences in physical activity, as cardiorespiratory fitness seems to be a valid indicator of cardiovascular health regardless of body mass index (Lavie et al., 2014; D. Lee et al., 2012). Cardiorespiratory fitness has indeed long been known to reduce mortality (Blair et al., 1989). While vigorous exercise may temporarily raise the risk of SCA, the effect is outweighed by the cardioprotective properties of regular exercise, both moderate and vigorous (Aune et al., 2020; Lemaitre et al., 1999; Siscovick et al., 1984). According to a prospective study of over 100,000 women, current cigarette smokers have a 2.44-fold risk of SCD compared to never-smokers (Sandhu et al., 2012). The risk of SCA increased with duration of smoking, and after cessation, it continued to be elevated for another 20 years. High caffeine consumption has been observed to associate with SCA in never-smokers (Weinmann et al., 1997). A Mediterranean diet has been reported to have a borderline inverted association with SCA compared to a Southern-style diet which includes larger amounts of added fat and sugar (Shikany et al., 2021). Individual foods, such as fish and nuts, also have apparent cardioprotective effects, whereas saturated fatty acids and free fatty acids have been associated with an increased risk of SCA (Albert et al., 2002; Chiuve et al., 2012; Jouven et al., 2001; Mozaffarian, 2008). During acutely stressful events, such as natural disasters, an excess of cardiovascular deaths has been observed (Kark et al., 1995; Trichopoulos et al., 1983). Takotsubo CM may contribute to this observation (Toni et al., 2019). Finally, certain types of air pollution have been suspected of increasing the risk of SCA (Dennekamp et al., 2010).

The risk factors for CAD and ischemic SCA have been studied extensively, whereas the risk factors for NIHD and subsequent SCA are not as well specified – partly due to the fact that NIHD consists of such different entities. As many NIHDs

are inherited or familially clustered, genetic factors might be a more significant contributor in nonischemic versus ischemic SCA. However, the traditional cardiovascular risk factors such as hypertension, obesity and alcohol consumption often induce NIHD as well and are common in nonischemic SCD victims (Hookana et al., 2011). Thus, similar advice, such as a Mediterranean diet, regular physical activity, cessation of smoking and heavy drinking, and proper treatment of existing medical conditions, ought to be sufficient to reduce the risk of nonischemic as well as ischemic SCA.

3 Aims of the study

The aim of the study was to examine nonischemic SCA in relation to psychotropic medication, alcohol abuse and non-shockable initial recorded rhythm. The specific aims of the study were:

1. To examine the relationship between non-shockable initial rhythm and NIHD at the time of SCA (Publication I)
2. To evaluate the association of the use of psychotropic medication with non-shockable initial rhythm at the time of SCA (Publication II)
3. To examine the use of psychotropic medication in victims of nonischemic SCD in comparison to the general population (Publication IV)
4. To assess the prevalence of elevated blood alcohol level in victims of nonischemic SCD (Publication III)

4 Materials and methods

4.1 Survivors of sudden cardiac arrest (I, II)

Study populations in studies I and II were derived retrospectively from the emergency service records of Oulu University Hospital (Oulu, Finland). The original data included 659 cases of SCA with a documented ECG rhythm at the time of SCA. All cases occurred between the years 2007 and 2012. The emergency medical service system is responsible for a population of about 741,000 inhabitants in the Northern Ostrobothnia Hospital District and is equipped with ambulances, a medical helicopter and a mobile unit with an emergency physician on board. The ECG rhythm was recorded at the scene by emergency personnel. The 2004 Utstein recommendation for uniform reporting of cardiac arrest was used for documenting the emergency service data (Jacobs et al., 2004), which included the delay from collapse to recording of rhythm, the initial rhythm, and patient outcome.

Subjects with a more than 30-minute delay from collapse to recording of rhythm and subjects with a non-cardiac cause for collapse were excluded, leaving us with a study population of 274 subjects of witnessed SCA in study I. Out of these subjects, 134 were victims of SCD and 140 were successfully resuscitated. In study II, the study population consisted of 222 cases of SCA, as we additionally excluded subjects with no information on pharmacotherapy during the 2-year period prior to SCA. Study II included 116 victims of SCD and 106 survivors of SCA. The selection of the study population in studies I and II is illustrated in Figure 8. The underlying heart disease of the survivors was defined by previous medical history and thorough clinical examination including coronary angiography and echocardiography. Information on prior mediation was acquired from the medical records of Oulu University Hospital electronic archives. All victims of SCD included in studies I and II were also part of the Fingesture study. SCA and SCD were defined to be of cardiac cause in all studies, and cases with non-cardiac reason for collapse or death, such as trauma, pulmonary embolism or intoxication, were not included in the studies.

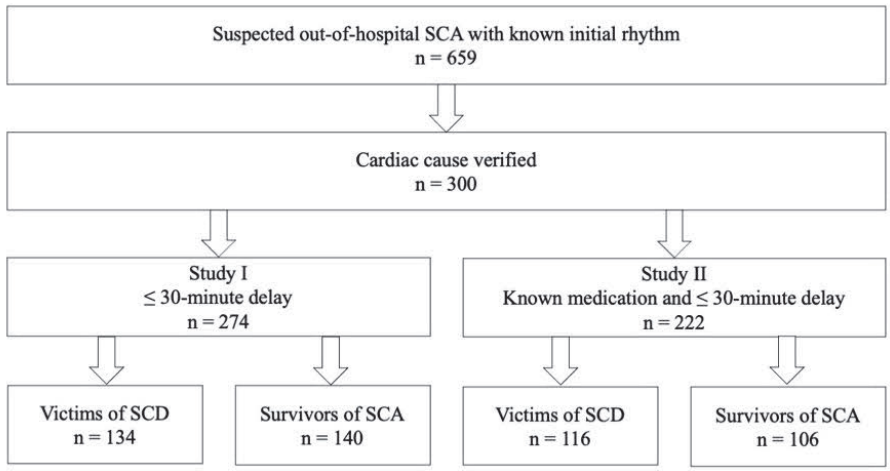

Fig. 8. Flow chart of the study population in studies I and II.

4.2 Victims of sudden cardiac death: the Fingesture study (I-IV)

The Fingesture study was designed in 1998 in order to examine the characteristics of victims of SCD in the Province of Oulu, Northern Finland. The study contains a total of 5,869 (mean age 65±12, 79% males) consecutive cases of SCD, all of which occurred between the years 1998 and 2017 in a specific geographical area in Northern Finland. Victims of non-cardiac sudden death were not included in the original study population. All victims were autopsied by forensic pathologists in the Department of Forensic Medicine of the University of Oulu and Finnish Institute for Health and Welfare, Oulu, Finland. According to Finnish law, medico-legal autopsy must be performed on all victims of sudden death if the death is not due to a known disease, the person was not treated by a physician during their last illness, or the death was otherwise unexpected. In previous literature, a death has been defined as sudden if it was witnessed within an hour after the onset of symptoms, or it was unwitnessed but happened within 24 hours of the person being last seen alive (Adabag et al., 2010). However, in this thesis, a death was considered sudden if it was witnessed within 6 hours after the onset of symptoms or the person was seen alive less than 24 hours ago. This timeframe has been used in some previous studies (Taylor et al., 2000) and was chosen in order to include as many cases of SCD as possible, as several cases might be missed with the original 1-hour timeframe suggested in 1982 (Hinkle & Thaler, 1982). The cause of death was

confirmed with autopsy in all cases, which greatly reduces the possibility of false SCD diagnoses. In studies III and IV, 4,392 cases of SCD due to ischemic heart disease were also excluded, leaving us with 1,477 victims of nonischemic SCD. In study III, after excluding 176 subjects with no information on blood alcohol level, the study population included 1,301 victims of nonischemic SCD. Study IV included 1,404 subjects of nonischemic SCD after excluding 73 subjects with no information on the use of psychotropic medication and no toxicology. The selection of the study population in studies III and IV is illustrated in Figure 9.

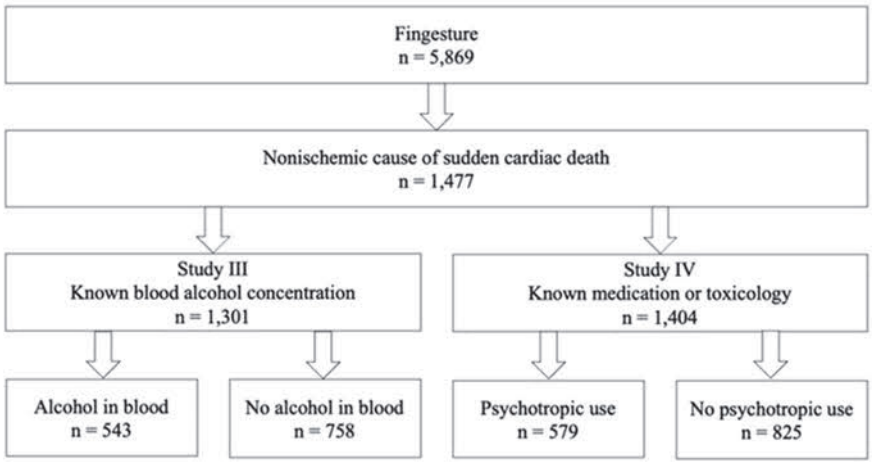

Fig. 9. A flow chart of the study population in studies III and IV.

4.3 Determination of cause of death (III, IV)

The causes of SCD were reported according to the ICD-10 code classes and defined based on a combination of autopsy reports, which included a death certificate and previous medical records, and questionnaires to closest relatives. A detailed classification of the causes of death was given according to more specific findings in autopsy, and medical records and questionnaires to relatives were also considered. The subtypes of NIHD were classified as hypertensive CM, obesity CM, alcoholic CM, fibrotic CM, dilated CM, hypertrophic CM, myocarditis, valvular heart disease, arrhythmogenic right ventricular CM, anomalous coronary arteries, unspecified CM and structurally normal heart. Limited genotyping for Finnish founder mutations of LQTS was performed to victims with no definable

structural basis for SCD. The criteria for these diagnoses are reported in Table 2 and have also been discussed in previous Fingesture studies (Hookana et al., 2011). The underlying heart disease was known before death in only 1 in 3 cases.

About 20% of all ~54,000 victims of death are autopsied each year in Finland, and toxicological analysis is performed in more than 6,500, or 12%, of all cases of death (Launiainen & Ojanperä, 2014; Statistics Finland, 2019). Average timeframes are 5 days from death to autopsy and 2–3 weeks from death to toxicology screening (Launiainen & Ojanperä, 2014). All autopsies included histologic examination. Toxicologic investigation was performed if autopsy results were insufficient to define the cause of death or toxic exposure was suspected. We utilized the toxicologic analyses which measured ethanol and medication concentrations from post-mortem femoral blood. Cases of intoxication were not included in the study. The blood ethanol level was determined by gas chromatography, and ethanol concentrations ≥ 0.02% were considered elevated/positive.

In study III, the term "heavy drinker" was used of individuals who consumed large amounts of alcohol regularly. This information was achieved from medical records, and the Finnish definition of excessive drinking, ≥ 24 regular drinks per week for men and ≥ 16 for women, was probably considered as a reference for heavy drinking.

The medications observed in study IV included benzodiazepines, antidepressants and antipsychotics. Information on medication usage was derived from toxicologic analyses and medical records. Subjects were only excluded if neither toxicology nor medical records were available. Both data were available in 67% of the study population; out of these, both data gave the same results in 83% of the cases. Information on medication use in the general Finnish population was derived from the Finnish Statistics on Medicines 2018 (Finnish Medicines Agency & Social Insurance Institution, 2018) and presented as defined daily dose/1000 inhabitants/day. The defined daily dose is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (World Health Organization, 2021).

The studies comply with the declaration of Helsinki and were approved by the ethics committee of Northern Ostrobothnia Hospital district (Oulu University Hospital). The Finnish Institute for Health and Welfare and the Regional State Administrative Agency of Northern Finland approved the review of medico-legal autopsy data.

Table 2. Autopsy-based definitions of the subtypes of nonischemic heart disease.

Causes of nonischemic SCD	Definition of the subtype of NIHD based on autopsy
Hypertensive CM	LVH, increased heart weight, unspecific fibrosis, other organ changes related to hypertension (e.g. arterial medial hypertrophy, intimal fibrosis in renal arterioles).
CM related to obesity and unspecified CM	LVH or both left and right ventricular wall hypertrophy, increased heart weight, dilation of ventricles and atria, excessive epicardial and myocardial fat, obesity.
Alcoholic CM	LVH, increased heart weight and focal replacement fibrosis of the myocardium. In later stages, signs of dilated CM, other organ changes related to excessive long-term alcohol consumption (e.g. liver cirrhosis and/or severe steatosis, pancreatic fibrosis).
Fibrotic CM	Interstitial, diffuse or patchy myocardial fibrosis without LVH, myocardial scarring or other apparent cause for fibrosis.
Dilated CM	Left ventricular dilation with inadequate degree of LVH. In later stages, pale and flabby myocardium and dilation of ventricles and atria, unspecific fibrosis and focal atrophy or hypertrophy of myocytes.
Hypertrophic CM	Concentric LVH with myocyte disarray and various degrees of interstitial fibrosis, often asymmetrical septal hypertrophy.
Myocarditis	Inflammatory infiltration of the myocardium with necrosis and/or degeneration of the adjacent myocytes.
Valvular heart disease	Aortic or mitral valve calcification
ARVC	Right ventricular dilation, right ventricular myocardial atrophy with fibrofatty replacement of myocytes.
Anomalous coronary arteries	Anomalies of origination, course or termination. Anomalous collateral vessels, anomalies of intrinsic coronary arterial anatomy.
Structurally normal heart	Macroscopically and microscopically normal heart with or without long QT syndrome mutations

ARVC = Arrhythmogenic right ventricular cardiomyopathy, CM = cardiomyopathy, LVH = left ventricular hypertrophy

4.4 Statistical analysis

Categorical variables are presented as percentage (%) of subjects. Chi-square test was used to assess differences in the distribution of dichotomized variables. Continuous variables with normal distribution are presented as mean±standard deviation (SD) and continuous variables with non-normal distribution as median (1^{st} – 3^{rd} quartile). Gaussian distribution of variables was evaluated by skewness test. When comparing continuous variables of two groups, independent samples t-test was used for variables with normal distribution and Mann-Whitney test for variables with non-normal distribution. In study I, when comparing continuous variables of three study groups (VF/VT vs. asystole vs. PEA), ANOVA analysis with post hoc Bonferroni correction was used for variables with normal distribution and Kruskal-Wallis test with Bonferroni correction for variables with non-normal distribution. Binary logistic regression analysis was used to determine the ORs for risk of non-shockable rhythm for subjects with ischemic or nonischemic SCA in study I and users of different psychotropic medication in study II. ORs are presented as OR, 95%CI.

All analyses were performed with the IBM Statistical Package for Social Studies 25–27 (SPSS Inc., Chicago, IL). Two-sided p-values < 0.05 were considered statistically significant.

5 Results

5.1 Initial rhythm and risk of sudden cardiac arrest (I, II)

Study I included 274 subjects (mean age 65±14 years, 78% males) with a known initial rhythm at the time of SCA. After excluding subjects with no information on medication use, study II included 222 subjects (mean age 64±14 years, 78% males). The delay from collapse to recording of rhythm was 9 (2–14) minutes in study I and 9 (1–12) minutes in study II. The distributions of initial rhythms in studies I and II are shown in Table 3. In both study populations, subjects with VF/VT were younger than subjects with asystole/PEA. There were more males in the VF/VT group compared to the asystole/PEA group in both studies. The delay from collapse to recording of rhythm was similar in the VF/VT and asystole/PEA groups. The underlying heart disease was more frequently ischemic in the VF/VT group compared to the asystole/PEA group in both studies. Asystole/PEA rhythm was associated with death as outcome in both studies (Table 3). No difference in age, gender or type of underlying heart disease was detected between victims of SCD and survivors of SCA in either study (Table 4). The delay from collapse to recording of rhythm was longer in victims of SCD compared to survivors in both studies.

5.1.1 Nonischemic heart disease and initial rhythm at the time of sudden cardiac arrest (I)

In study I, we also compared subjects with VF/VT, asystole and PEA separately. Subjects with VF/VT were significantly younger than subjects with PEA (63±13 years versus 71±11 years, $p = 0.005$). There were more males in the VF/VT group compared to the PEA group (84% versus 66%, $p = 0.026$). There were no significant differences when comparing other groups to the asystole group (mean age 65±15 years, 74% males). The delay from collapse to recording of rhythm was similar in the VF/VT group (8 [3–12] minutes) compared to the asystole group (10 [4–15] minutes, $p = 0.148$) and the PEA group (1 [0–12] minutes, $p = 0.288$). The delay was shorter in the PEA group compared to the asystole group ($p = 0.011$).

The cause of SCA was ischemic in 216 (79%) subjects and nonischemic in 58 (21%) subjects. Ischemic SCA subjects were older than subjects with SCA due to NIHD (Table 5). There was a trend towards more males in the ischemic versus nonischemic subjects. The delay was shorter in ischemic subjects (Table 5).

Table 3. Characteristics of the study populations and rhythm subgroups in studies I and II.

Characteristics	Study I				Study II			
	Total	VF/VT	Asystole/PEA	P-value	Total	VF/VT	Asystole/PEA	P-value
	n = 274	n = 149	n = 125		n = 222	n = 123	n = 99	
Age, years (mean±standard deviation)	65±14	63±13	67±15	0.035	64±14	62±13	67±15	0.028
Gender, male	78%	84%	71%	0.011	78%	84%	71%	0.020
Delay, minutes (median [1st – 3rd quartile])	9 (2–14)	8 (3–12)	10 (1–15)	0.445	9 (1–13)	8 (3–12)	10 (0–14)	0.780
Underlying heart disease, ischemic	79%	86%	70%	0.002	77%	85%	68%	0.003
Outcome of SCA, death	49%	31%	70%	<0.001	52%	32%	78%	<0.001

PEA = pulseless electrical activity, VF = ventricular fibrillation, VT = ventricular tachycardia.

Table 4. Characteristics of the study populations and outcome subgroups in studies I and II.

Characteristics	Study I				Study II			
	Total n = 274	Victims of SCD n = 149	Survivors of SCA n = 125	P-value	Total n = 222	Victims of SCD n = 123	Survivors of SCA n = 99	P-value
Age, years (mean±standard deviation)	65±14	65±14	65±14	0.986	64±14	64±14	64±14	0.833
Gender, male	78%	79%	77%	0.695	78%	78%	78%	0.898
Delay, minutes (median [1st – 3rd quartile])	9 (2–14)	10 (4–15)	7 (0–11)	0.004	9 (1–13)	10 (3–15)	7 (0–11)	0.020
Underlying heart disease, ischemic	79%	75%	82%	0.170	77%	73%	81%	0.165

SCA = sudden cardiac arrest, SCD = sudden cardiac death.

Table 5. Characteristics of the study population I according to the type of underlying heart disease.

Characteristics	Total n = 274	Ischemic n = 216	Nonischemic n = 58	P-value
Age, years (mean±standard deviation)	65±14	67±13	57±16	<0.001
Gender, male	78%	81%	70%	0.058
Delay, minutes (median [1st – 3rd quartile])	9 (2–14)	8 (1–13)	10 (7–15)	0.014

Asystole was significantly more common in subjects with NIHD compared to subjects with ischemic heart disease (47% versus 28%, p = 0.006). VF/VT, on the other hand, was associated with ischemic cause of SCA (nonischemic 36% versus ischemic 59%, p = 0.002). No significant association was found between PEA and type of underlying heart disease (nonischemic 17% versus ischemic 13%, p = 0.403). In a univariate logistic regression model, SCA due to NIHD was significantly associated with asystole/PEA rhythm (OR 2.56, 95%CI 1.41–4.67, p = 0.002) and the association remained even after adjusting for age, gender and delay from collapse to recording of rhythm (OR 3.2, 95%CI 1.67–6.50, p = 0.001).

5.1.2 Psychotropic medication and initial rhythm at the time of sudden cardiac arrest (II)

Out of all subjects in study II, 36 (16%) were users of psychotropic medication. More precisely, 17 (8%) subjects were users of benzodiazepines, 20 (9%) of antidepressants, 16 (7%) of antipsychotics, and 15 (7%) of multiple types of psychotropic medication (Table 6). Use of psychotropic medication, as well as use of benzodiazepines, antidepressants and antipsychotics, was associated with asystole/PEA rhythm. Use of all psychotropic medication groups, including use of multiple types of psychotropic medicine, was associated with a fatal outcome of SCA (Table 6).

Post-mortem blood analysis was performed in 37% of 116 victims of SCD. Out of these 43 cases, 15 (35%) had psychotropic medication in post-mortem blood. The type of medication detected in blood was benzodiazepines in 12 (28%) subjects, antidepressants in 6 (14%) subjects, antipsychotics in 4 (9%) subjects, and multiple types in 8 (19%) subjects. Presumed use of medication and the result of the post-mortem blood analysis matched in 79% of the cases in which blood analysis was performed.

Table 6. Medication use according to initial rhythm and outcome of sudden cardiac arrest in study II.

Type of medication	Total n = 222	VF/VT n = 123	Asystole/PEA n = 99	P-value	Victims of SCD n = 116 (52)	Survivors of SCA n = 106 (48)	P-value
Psychotropic medication	36 (16%)	10 (8%)	26 (26%)	< 0.001	27 (23%)	9 (9%)	0.003
Benzodiazepines	17 (8%)	5 (4%)	12 (12%)	0.023	14 (12%)	3 (3%)	0.009
Antidepressants	20 (9%)	6 (5%)	14 (14%)	0.015	15 (13%)	5 (5%)	0.031
Antipsychotics	16 (7%)	4 (3%)	12 (12%)	0.011	13 (11%)	3 (3%)	0.016
Multiple types of psychotropics	15 (7%)	5 (4%)	10 (10%)	0.075	13 (11%)	2 (2%)	0.006

PEA = pulseless electrical activity, VF = ventricular fibrillation, VT = ventricular tachycardia, SCA = sudden cardiac arrest, SCD = sudden cardiac death.

In a logistic regression model, with and without adjusting for age, gender and underlying heart disease, use of psychotropic medication was independently associated with asystole/PEA rhythm at the time of SCA (Table 7). In a separate analysis of subtypes of psychotropic medication, use of antipsychotics was also associated with asystole/PEA before and after adjustments. Use of benzodiazepines or antidepressants was associated with asystole/PEA rhythm, but the association was not significant after adjustments (Table 7).

In another logistic regression model, use of psychotropic medication was associated with death at the time of SCA (OR 3.27, 95%CI 1.46–7.33, p = 0.004), but the association was not significant after adjusting for asystole/PEA rhythm and delay from collapse to rhythm recording (OR 1.83, 95%CI 0.74–4.53, p = 0.189).

Table 7. Medications as determinants of the initial rhythm in study II.

Type of medication	Risk for asystole/PEA without adjustments, OR (95%CI)	P-value	Risk for asystole/PEA with adjustments, OR (95%CI)[a]	P-value
Psychotropics	4.02 (1.83–8.84)	0.001	3.18 (1.40–7.23)	0.006
Benzodiazepines	3.29 (1.12–9.69)	0.030	3.00 (0.96–9.35)	0.058
Antidepressants	3.25 (1.20–8.80)	0.020	2.11 (0.73–6.15)	0.170
Antipsychotics	4.10 (1.28–13.15)	0.018	4.27 (1.28–14.25)	0.018

CI = confidence interval ([a]adjusted for gender, age and underlying heart disease), OR = odds ratio, PEA = pulseless electrical activity.

5.2 Acute alcohol intake and nonischemic sudden cardiac death (III)

A total of 1,301 victims of nonischemic SCD (mean age 57±12, 78% males) were included in study III. Alcohol was found in post-mortem blood in 543 (42%) subjects, out of which the concentration of ethanol was ≥ 0.10% in 339 (62%) subjects and ≥ 0.15% in 252 (46%) subjects. The concentration of alcohol in subjects with positive blood alcohol analysis is illustrated in Figure 10. The characteristics of the study population and the groups with and without alcohol in blood are presented in Table 8. Male sex, history of hypertension and fatty liver in autopsy were more common in subjects with alcohol in blood. No significant differences were found in age, body mass index, history of diabetes or hepatic cirrhosis in autopsy between the groups. Out of all victims, 664 (51%) were known to be heavy drinkers. Victims with elevated blood alcohol level were more often heavy drinkers compared to victims with no alcohol in blood (61% versus 44%, p < 0.001).

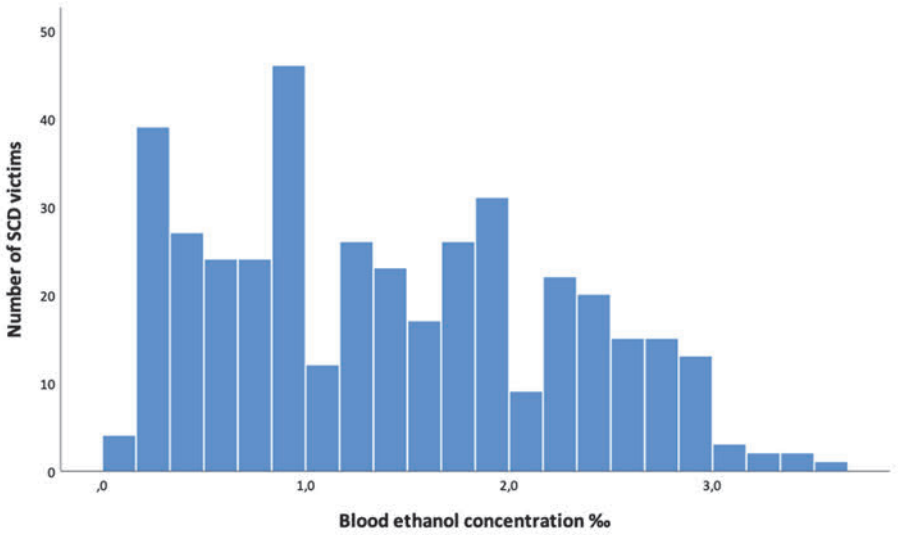

Fig. 10. Blood ethanol concentration in 543 victims of sudden cardiac death with alcohol in blood.

Table 8. Characteristics of the study population III and subgroups.

Characteristics	Total n = 1,301	Alcohol in blood n = 543 (42%)	No alcohol in blood n = 758 (58%)	P-value
Age, years (mean±standard deviation)	57±12	58±11	56±13	0.067
Gender, male	78%	83%	74%	<0.001
BMI, kg/m^2 (mean±standard deviation)	30±8.1	30±7.8	30±8.3	0.747
Diabetes	19%	20%	19%	0.925
Hypertension	42%	47%	39%	0.007
Moderate or severe fatty liver in autopsy	57%	63%	53%	<0.001
Hepatic cirrhosis in autopsy	34%	37%	32%	0.067

BMI = body mass index.

The causes of death in the study population and subgroups are shown in Table 9. The most prevalent cause was hypertensive CM (27%), followed by CM related to obesity (24%), alcoholic CM (22%) and fibrotic CM (13%). LQTS mutation was detected in 4 out of 13 subjects with a structurally normal heart. Hypertensive CM, fibrotic CM, myocarditis and valvular heart disease were associated with elevated blood alcohol level (Table 9). A borderline association was observed between alcoholic CM and ethanol in blood. Heavy drinking was strongly associated with

alcoholic CM as the cause of death ($p < 0.001$). Out of 289 victims with alcoholic CM, 285 (99%) were known heavy drinkers.

Table 9. Types of underlying nonischemic heart disease in subjects with alcohol in blood and subjects with no alcohol in blood in study III.

Type of heart disease	Total n = 1,301	Victims with alcohol in blood n = 543	Victims with no alcohol in blood n = 758	P-value
Hypertensive CM	351 (27[a])	162 (46[b])	189 (54[c])	0.050
CM related to obesity	307 (24)	135 (44)	172 (56)	0.363
Alcoholic CM	289 (22)	135 (47)	154 (63)	0.052
Fibrotic CM	170 (13)	58 (34)	112 (66)	0.031
DCM	39 (3)	13 (33)	26 (67)	0.280
HCM	30 (2)	14 (47)	16 (53)	0.580
Myocarditis	46 (4)	9 (20)	37 (80)	0.002
Valvular heart disease	44 (3)	10 (23)	34 (77)	0.009
ARVC	5 (0)	3 (60)	2 (40)	0.655
Anomalous coronary arteries	4 (0)	0 (0)	4 (100)	0.145
Other nonischemic heart disease	3 (0)	0 (0)	3 (100)	0.270
Structurally normal heart	13 (1)	4 (31)	9 (69)	0.575

ARVC = arrhythmogenic right ventricular cardiomyopathy, CM = cardiomyopathy, DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy.

[a]Percentage of cause of death among all victims.

[b]Percentage of cases with alcohol in blood.

[c]Percentage of cases with no alcohol in blood.

5.3 Psychotropic medication and nonischemic sudden cardiac death (IV)

Study IV consisted of 1,404 victims of nonischemic SCD (mean age 57±13, 77% males), out of which 579 (41%) used psychotropic medication. Victims with psychotropic medication were younger and more often female compared to victims with no psychotropic use (Table 10). Victims with psychotropic medication also had a higher body mass index and a smaller heart weight in autopsy. There was no difference in the history of hypertension between the groups (Table 10).

The study population included 378 (27%) users of benzodiazepines, 265 (19%) of antidepressants, 257 (18%) of antipsychotics and 260 (18%) users of multiple types of psychotropic medication. Calculated from the defined daily dose/1,000 inhabitants/day index, 12% of the Finnish population were users of psychotropic medication, 2.3% of benzodiazepines, 7.5% of antidepressants and 2.2% of antipsychotics (Table 11). Use of psychotropics in general, as well as all medication

subgroups, was significantly more common in the study group compared to the general population (Table 11).

Table 10. Characteristics of the study population IV and subgroups.

Characteristics	Total n = 1,404	Psychotropics n = 579	No psychotropics n = 825	P-value
Age, years (mean±standard deviation)	57±13	56±12	59±13	< 0.001
Gender, male	77%	72%	81%	< 0.001
BMI, kg/m^2 (mean±standard deviation)	28 (24–34)	29 (25–35)	28 (24–33)	0.002
Hypertension	43%	44%	42%	0.456
Heart weight in autopsy, grams (mean±standard deviation)	496±146	483±141	495±149	0.006

BMI = body mass index.

Table 11. Use of psychotropic medication in the study group versus general population.

Type of medication	Total n = 1,404	General population n = 1,000	P-value
Psychotropic medication	579[a] (41%)	120[b] (12%)	< 0.001
Benzodiazepines	378 (27%)	23 (2.3%)	< 0.001
Antidepressants	265 (19%)	75 (7.5%)	< 0.001
Antipsychotics	257 (18%)	22 (2.2%)	< 0.001

[a]Number of users.

[b]Number of users estimated by defined daily doses.

6 Discussion

6.1 Sudden cardiac arrest in nonischemic heart disease

SCD remains the most common mode of death in Western countries (C. X. Wong et al., 2019). Extensive efforts have been made to improve the chain of survival as well as the prevention and treatment of CAD (Chugh, 2017; Yu et al., 2020). As a result, the incidence of SCA seems to be declining, although the findings are not consistent (C. X. Wong et al., 2019). More specifically, the incidence of ischemic SCA is declining, but the incidence of SCA from NIHD seems to have remained on the same level (Bunch & White, 2005; Väyrynen et al., 2011). Thus, the nonischemic proportion of SCA victims has increased (Junttila et al., 2016).

The mechanisms and contributing factors of nonischemic SCA are still largely unknown. The challenge in comparing our studies to previous literature has partly resulted from the heterogeneous definitions and uses of CMs and NIHD. As mentioned earlier, neither the 2007 ESC position statement nor the 2006 AHA scientific statement supported a broader CM classification including valvular or hypertensive CM (Elliott et al., 2008; Maron et al., 2006). The exclusions were mainly based on clinical differences in diagnosis and management (Elliott et al., 2008). CM is indeed often diagnosed for clinical purposes, such as initiating treatment and preventing adverse events, and the diagnosis is mostly based on echocardiography findings (E. M. McNally & Mestroni, 2017). Using both clinical history and autopsy findings in SCA research might reveal more complex etiologies and mechanisms of CMs than the established definitions allow. Due to legal reasons, many autopsy-verified SCD studies are biased towards young people; however, in Finland, virtually all sudden death victims are autopsied. In the Fingesture study, the established CM types represented only a minority of nonischemic SCD victims with structural myocardial changes, suggesting that lifestyle factors affected the prognosis of CM in most cases. Excluding these victims from the definition of CM, as is the custom, might have substantially biased the results.

Some, but not all studies have reported an increase in the mean age of SCA victims, which may have partly resulted from more efficient prevention and treatment of heart disease (Chan et al., 2014; Herlitz et al., 2000; Junttila et al., 2016; Strömsöe et al., 2015). The mean age of SCA victims is usually higher in urban cohort studies examining the predictors and outcomes of out-of-hospital SCA than in autopsy-based SCD studies (Marshall & Milikowski, 2017; Sasson et al.,

2010; Spain, 1960). In studies I and II, which were constructed using emergency service records, the mean age of the participants was similar to the usual 65–70-year observation (Sasson et al., 2010). The high autopsy rate in our studies probably reduced the usual selection bias towards younger victims and resulted in a rather typical mean age in the Fingesture study. Interestingly, postmortem SCD studies based on death certificates, with or without partial autopsy verification, often have a similar or even higher mean age compared to resuscitation studies (Chugh et al., 2004; Zheng et al., 2001).

Out of the initial rhythms during SCA, previous research has mostly concentrated on preventing and treating VF, which can often be defibrillated, resulting in a superior survival rate compared to asystole and PEA (B. McNally et al., 2011). The proportions of asystole and PEA during SCA have increased, and together they occur nowadays in more than half of SCA cases (Hulleman et al., 2012). SCA victims with VF/VT have been observed to be younger than those with asystole or PEA (Ko et al., 2016), which was also seen in studies I and II. Another similarity of studies I and II to previous data is the higher proportion of males in victims with VF/VT (Ko et al., 2016). Previous studies have reported similar delays from collapse to recording of rhythm between the rhythm groups (Engdahl et al., 2001; Teodorescu et al., 2010). Thus, the delay has not been viewed as a cause of non-shockable rhythms. In studies I and II, however, subjects with asystole had a longer delay compared to those with VF/VT, indicating that asystole might in some cases be the result of untreated VF. This phenomenon might not be as widely present in PEA patients, as they had an even shorter delay compared to those with VF. The delay was also shorter in survivors compared to victims of SCD, which underlines the importance of the chain of survival. In studies I and II, asystole/PEA rhythm was associated with death as outcome compared to VF/VT, which also aligned with previous research (Ko et al., 2016).

Relatively little knowledge is available concerning the underlying heart disease in SCA victims with asystole or PEA. In study I, asystole was associated with NIHD, while PEA was not. In a logistic regression model, SCA due to NIHD was associated with asystole/PEA. VF/VT was associated with CAD, aligning with previous studies (Teodorescu et al., 2010). The declining incidence of VF has been attributed to the remarkable decrease of both sudden and nonsudden death from CAD in the past few decades (Cobb et al., 2002; Fox et al., 2004). The increasing proportion of asystole and PEA might at least in part be explained by the decrease of VF and SCA, but other causes have also been hypothesized (C. X. Wong et al., 2019). The advances in cardiovascular treatments, followed by the apparent

increasing age of SCA victims, has resulted in rising numbers of end-stage cardiovascular disease and accumulating risk factors, some of which may predispose and individual to asystole or PEA (Hayashi et al., 2015). The proportion of unwitnessed arrests, in which a shockable rhythm may progress to asystole before assessment of rhythm, has been reported to have increased (Hayashi et al., 2015). There have also been contradictory results (Strömsöe et al., 2015). The increasing use of beta-blockers, which has been reported as a risk factor for PEA compared to VF, may have contributed to the trend (Youngquist et al., 2008). Although the proportion of asystole and PEA has increased, it is unclear whether the incidences of asystole and PEA have declined, remained on the same level, or increased (Andrew et al., 2014; Bergström et al., 2018; Bunch & White, 2005; Cobb et al., 2002). However, the changing epidemiology of SCA poses a new challenge for both researchers and clinicians, as there is a paucity of efficient strategies in the prevention and treatment of non-shockable rhythms during SCA (Hayashi et al., 2015; Myerburg et al., 2013).

Psychotropics, especially antipsychotics, have repeatedly been reported to increase the risk of SCA (Honkola et al., 2012; Ray et al., 2001, 2009). At first, atypical antipsychotics seemed to have milder cardiovascular risks compared to typical antipsychotics, but research indicates that the risks are actually quite similar, with the exception of drug-specific differences in both groups (Beach et al., 2018; T. A. Manolis et al., 2019; Ray et al., 2009). Benzodiazepines seem rather safe for the heart as they have no acknowledged proarrhythmic potential (Kovacs & Arora, 2008; A. S. Manolis, 2017; C. K. Wu et al., 2014). Antidepressants, on the other hand, have been reported to increase the risk of SCA (Honkola et al., 2012; Kovacs & Arora, 2008; Teodorescu et al., 2013). In study II, the use of psychotropics and antipsychotics was associated with asystole/PEA rhythm during SCA before and after adjustments. Benzodiazepines and antidepressants were associated with asystole/PEA, but the association was not significant after adjustments. The mechanisms of these associations are still largely unknown.

The relationship of psychotropic medication and the initial rhythm during SCA has not been widely studied. The Oregon Sudden Unexpected Death Study reported an increase in the risk of PEA versus VF/VT in users of antidepressants and antipsychotics (Teodorescu et al., 2013). Individuals with asystole as the initial rhythm were not included in the study. Study II aligns with these results, suggesting that the use of psychotropics might induce both asystole and PEA during SCA, thus reducing the probability of survival. The cardiac risks of psychotropics are usually attributed to their QT-prolonging properties. QT prolongation is, however,

considered a risk factor for VF/VT rather than asystole or PEA. Instead, the relationship might be explained by the negative inotropic and hypotensive effects of psychotropics, as contractile failure is an essential mechanism of PEA (Kovacs & Arora, 2008; T. A. Manolis et al., 2019; Myerburg et al., 2013). Psychotropics may also cause conduction disturbances, such as a third degree atrioventicular block, which is a common mechanism of asystole (O'Brien & Oyebode, 2003). Further research is needed to clarify the mechanisms of the possible causal relationship of psychotropics and asystole/PEA.

While the use of psychotropics has been associated with an increased risk of SCD in patients with CAD (Honkola et al., 2012; Thorogood et al., 1992), similar studies are scarce in patients with NIHD. In study IV, two in five nonischemic SCD victims were users of psychotropic medication. The use of psychotropic drugs in general, as well as in all medication subgroups, was more common in nonischemic SCD victims compared to the general population. Previous, smaller autopsy studies have reported a high prevalence of NIHD in SCD victims who used psychotropic drugs (Frassati et al., 2004; Mehtonen et al., 1991). In the general population, only 12% were estimated to use psychotropics. Similar and lower usages in the general population have been reported around the globe (Raschi et al., 2013; Stephenson et al., 2013; C.-S. Wu et al., 2012). In some cases, psychotropic drugs can cause NIHD, such as in clozapine-induced CM, which may lead to SCD (Ronaldson et al., 2015). Other antipsychotics and antidepressants have also been reported to induce CM (T. A. Manolis et al., 2019; Neil et al., 2012; Smolders & Smolders, 2017). Study II suggests that psychotropic medication might contribute to the onset of SCA in patients with NIHD. Most types of NIHD are characterized by myocardial fatty and/or fibrous tissue which makes the heart susceptible to arrhythmia via anatomical reentry, in which case the psychotropic drug could act as a transient risk factor. Reentry is also a key mechanism of most ventricular arrhythmias, although not specifically of torsades de pointes (Al-Khatib et al., 2018). Triggered activity and torsades de pointes can, however, also occur in nonischemic SCA (B. A. Steinberg et al., 2017). Future cohort or case-control studies might clarify the possible association of each psychotropic drug with nonischemic SCA as well as the related mechanisms.

In study III, an association between heavy drinking and alcoholic CM was perceived. Fatty liver was also a more common autopsy finding in victims with ethanol in blood than those without, suggesting a possibility of alcohol-related liver disease; however, the association did not extend to hepatic cirrhosis. Out of all types of NIHD, hypertensive CM, fibrotic CM, myocarditis and valvular heart

disease were associated with an elevated blood ethanol level, while alcoholic CM was not. Alcohol consumption can cause alterations in the immune system, which has been linked to myocarditis (Maisch, 2016). Light-to-moderate alcohol intake seems to lower the risk of aortic sclerosis and stenosis, whereas heavy drinking has not been reported to affect it (Larsson et al., 2017; Markus et al., 2015). Male sex was associated with a positive blood alcohol test. While men tend to drink more alcohol than women, alcohol abuse seems have more prominent effects on women due to physiological differences (Fernández-Solà et al., 1997; Tigerstedt et al., 2020).

In study III, as many as two out of five nonischemic SCD victims had alcohol in blood. Most studies about alcohol abuse and SCD have examined patients with ischemic heart disease, whereas similar studies concerning NIHD are scarce. One study reported an increased risk of SCD in heavy drinking men without diagnosed CAD, but the cause of death was not verified with autopsy (Wannamethee & Shaper, 1992). Study III suggests that acute alcohol intake might contribute to the onset of SCA in nonischemic victims. Given that the structural alterations of NIHD and the electrophysiological effects of alcohol can both induce arrhythmias, a synergic effect might explain the possible association, which may be further clarified by future research.

6.2 Clinical implications

Given that psychiatric conditions and psychotropics can both separately increase the risk of SCA (Beach et al., 2018; Li et al., 2018), clinicians should assess, and if possible, treat the cardiovascular risk factors of each psychiatric patient. The risk of SCD concerning psychotropic medications varies substantially among the medication groups as well as individual agents. In addition to the established usage in psychiatric conditions, psychotropics are increasingly often prescribed for off-label indications, resulting in additional concerns. An example of this is using psychotropic medication for insomnia, in which case the possibility of sleep apnea as an additional cardiac risk factor should be taken into consideration. Clinicians ought to acknowledge the effect of polypharmacy, psychiatric and other comorbidities, and existing, often undiagnosed heart disease on the cardiac risks in users of psychotropic medication. At the very least, the cardiovascular risks of each patient should be acknowledged before initiation of a psychotropic drug (Shah et al., 2014). ECG monitoring is often required before initiation and after reaching the therapeutic dose, especially in cases with preexisting heart disease or

cardiovascular symptoms, when prescribing drugs with a known risk of QT prolongation, or if the medication is to be used continuously.

Overall alcohol consumption in Finland has decreased by 21% between 2007 and 2019 (Tigerstedt et al., 2020). Binge drinking and underage drinking have both declined. Among older people, on the other hand, drinking has leveled out or even increased. Considering the accumulation of cardiac risk factors and comorbidities which often accompany aging, this is rather an unsettling trend. Clinicians ought to ask patients about their alcohol usage regularly and without judgment, especially if the patient has a diagnosed cardiovascular disease or symptoms such as dyspnea, chest pain or history of syncope. Questionnaires such as the Alcohol Use Disorders Identification Test, assembled by the World Health Organization, can be utilized in the process.

6.3 Strengths and limitations

Due to the high number of medico-legal autopsies in Finland, the Fingesture study offers an exceptional perspective to the causes and characteristics of SCD. The study populations in studies III and IV were of considerable size, a strength which did not reach its full potential due to the absence of adequate control groups. In studies I and II, on the other hand, the populations were smaller but suitable for logistic regression models.

Studies I and II took into account all possible rhythms during SCA. Many researchers tend to exclude cases with asystole on the basis of it sometimes being the end stage of other rhythms. In order to minimize this effect, we excluded cases with a more than 30-minute delay from collapse to recording of rhythm. Also, the delay was similar in cases of VF/VT and asystole. As asystole is nowadays responsible for approximately half of all SCA cases, we consider its inclusion a major asset in our first two studies (Andrew et al., 2014; Bergström et al., 2018). Given the substantially different epidemiologic features and mechanisms of asystole and PEA, they should, however, be studied as separate entities whenever possible. Due to the relatively small sample size in studies I and II, asystole and PEA could not be examined separately in all analyses. This limitation was observed especially in the analysis of different psychotropic medications in study II, as separating asystole and PEA would have greatly reduced the statistical power and thus limited the reliability of the study.

Studies II and IV also had several limitations concerning psychotropic medication. We could not take into account the dose or duration of medication use.

We also did not have information on psychiatric comorbidities, which have likewise been recognized to affect cardiac risks (Hennekens et al., 2005). In study II, we used medical records to assess the use of psychotropic drugs, which did not guarantee that the subjects were actually taking the medications. Long-term medication adherence has been reported at only about 50% in previous literature (Brown & Bussell, 2011). This issue was partly solved in study IV, in which we used toxicology results in addition to the medical records. However, in study IV, several other limitations emerged as a result of comparing our results to a public record. Our study population had quite distinct characteristics, such as age and sex, compared to the general population, which limited the number of possible comparisons. Defined daily doses were rough estimates of medication use and susceptible to biases due to overlapping of categories and variations in therapeutic doses, and thus probably more suitable for international or longitudinal comparisons.

Previous SCA studies have often compared the fatal outcome to survival to hospital discharge. Unfortunately, we did not have information about further conditions of the survivors in studies I and II, and thus only measured survival to hospital admission. As about 20–30% of all SCA victims survive to hospital admission and only 5–10% to hospital discharge (Chan et al., 2014; Gräsner et al., 2016; Teodorescu et al., 2010; M. K. Y. Wong et al., 2014; Yan et al., 2020), this may have resulted in a bias towards survivors, and also partly explains the higher-than-average survival rate in studies I and II.

In study III, no control group was present, limiting the available analyses. Also, we only addressed alcohol intake at the time of SCD, as previous alcohol usage could not be measured, apart from recognizing the known heavy drinkers. The victims with alcohol in blood were more often heavy drinkers, as anticipated; however, almost half of those without alcohol in blood were also heavy drinkers. Lastly, as toxicology analyses are not performed in all medico-legal autopsies, studies III and IV were susceptible to selection bias towards cases in which alcohol/medication exposure may have been suspected.

Nevertheless, we consider autopsy verification of all cases of SCD a major asset in all four studies. In previous studies, the cause of death has often been determined using previous medical records or death certificates, which might be less reliable compared to autopsy (Iribarren et al., 1998). Many sudden conditions, such as stroke, aortic dissection and massive pulmonary embolism may mimic SCD clinically and thus be falsely diagnosed as SCD. In our studies, all deaths were confirmed to be of cardiac cause by autopsy.

7 Conclusions

1. NIHD is associated with asystole/PEA rhythm at the time of SCA. The increasing nonischemic proportion of SCA might partly explain the increasing trend of asystole/PEA during SCA. (Publication I)
2. The use of psychotropic medication and especially antipsychotics is associated with initial asystole/PEA rhythm at the time of SCA. This might be one mechanism explaining the association of psychotropic medication with an increased risk of SCA. (Publication II)
3. The use of psychotropic medication is prevalent in victims of nonischemic SCD compared to the general Finnish population. The use of psychotropics might be a risk factor for SCA, not only in victims with CAD but also those with NIHD. (Publication IV)
4. Elevated blood alcohol level is common in Finnish victims of nonischemic SCD, especially in males. Recent alcohol consumption might contribute to the incident in many victims of nonischemic SCD. (Publication III)

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