Sudden cardiac arrest: Studies on risk and outcome

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CHAPTER 1

Introduction and outline
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Sudden cardiac arrest (SCA) is a leading cause of death in industrialized countries, affecting 180,000-250,000 individuals per year in the United States.\(^1,2\) In Europe, 275,000 out-of-hospital SCAs are treated by emergency medical services annually.\(^3\) The largest absolute number of SCA events occurs out-of-hospital in the general population in persons who are not considered to be at high risk for SCA. Although the majority of out-of-hospital SCAs (\(\approx 70\%\)) have a cardiac cause, in \(-50\%\) patients it is the first sign of a cardiovascular disease.\(^4,6\) Out-of-hospital SCAs are often lethal, with survival rates ranging from 3\% to 19\%.\(^7,9\) In the general population, SCA typically is the final outcome of a culmination of multiple factors. A combination of inherited and/or acquired disorders, stressors and circumstantial triggers eventually initiate an SCA. SCA victims in the general population are hence a very heterogeneous group to study.

In order to reduce the number of deaths due to SCA, two main approaches can be distinguished: 1) identify those at risk in order to prevent SCA, and 2) optimize out-of-hospital resuscitation care and in-hospital post-resuscitation care to improve survival after SCA.

Identifying risk factors of SCA

There are many ways to investigate the complex interplay of risk factors of SCA. These risk factors can be studied in the general population (applying to all) or in certain risk groups (persons with a higher a-priori risk). Risk factors may be sought at all levels: inherited and/or acquired factors, stressors and circumstantial triggers can play a role at the health care system level, in the direct social and physical environment of the person, and in the body itself, at system, organ or (sub)cellular level. Mechanisms playing at the (sub)cellular level may result in increased risk of a particular drug at the population level. Other mechanism may only play a role in certain patient groups and/or in certain situations. In many cases, SCA risk can be appreciated through a ‘multiple hit model’. This means that a given factor may be necessary but not sufficient; multiple factors need to coincide in order to initiate the cascade of events eventually leading to SCA. Knowledge about these interacting mechanisms may facilitate preventive measures to avoid lethal combinations of inherited and/or acquired risk factors. For example, a non-modifiable genetic risk factor may only become threatening in the presence of modifiable risk factors as medication use, stressors or disease. Informed advice to patients will enable them to avoid these combinations.

In order to explore proposed mechanisms involved in SCA risk, the risk of the occurrence of SCA itself can be studied, but also of markers of SCA risk, such as certain abnormalities at the electrocardiogram (ECG). For instance, can we see more ECG-abnormalities in a patient group that is known to have a higher risk of SCA when
compared to a control group? Or can the established effects on the ECG of a certain drug be recognized in a patient group that has multiple co-morbidities? Indeed, several ECG markers for SCA risk have been established in the general population; these include QTc-prolongation,\textsuperscript{10,11} a Brugada ECG-pattern\textsuperscript{12,13} and an early repolarization pattern (ERP).\textsuperscript{14} Studying ECGs from well-defined patient groups may provide insight into the mechanism underlying increased SCA risk. Also, it may provide insight into the importance of an established mechanism (i.e., QT-prolongation caused by potassium channel blocking drugs) in a certain population.

\textit{Survival after SCA}

The second approach to prevent deaths due to SCA is to improve survival chances after an SCA has occurred. This applies in particular to out-of-hospital cardiac arrest (OHCA), because the majority of lethal SCAs occur out-of-hospital, and survival gains of improved treatments are highest here. Determinants of survival after OHCA can be patient characteristics (including medical history), the setting and adequate recognition of the OHCA, and elements of the chain-of-care involved when resuscitation is initiated. Chances on survival are highest when an OHCA victim has a so-called shockable rhythm (ventricular fibrillation or ventricular tachycardia, VT/VF) when emergency medical services or a lay-rescuer with an automated external defibrillator (AED) arrive. Presence of a shockable initial rhythm depends on the direct cause of the OHCA, but also on timely recognition: while OHCA is usually caused by VF, VF will deteriorate into, mostly untreatable, asystole within minutes.

Early defibrillation is vital for survival after OHCA: survival rates of OHCA with VF decrease with every minute that defibrillation is delayed. In the Netherlands, recent initiatives to improve out-of-hospital care were primarily aimed at decreasing time to first shock delivery by more widespread use of the AED by dispatched rescuers (firefighter/police team) and by lay-rescuers using publicly available AEDs.\textsuperscript{15} Evaluation of these initiatives and other determinants of survival after OHCA are of vital importance in order to maximize outcome of resuscitation attempts.

\textit{Outline of the thesis}

It is not possible to address all issues at all levels concerning SCA at once. Nonetheless, the AmsteRdam REsuscitation STudies (ARREST), of which several projects are presented in this thesis, seeks to facilitate the study of SCA at all the levels mentioned above, if possible in interaction with each other. ARREST was set up to establish the determinants of outcome of OHCA and gain insight into the genetic, clinical and pharmacological determinants of OHCA in the general population. Its aims are deliberately set this wide since it recognizes that OHCA, both the risk of its occurrence and the odds of surviving from it, is a particularly multifactorial phenomenon.
This thesis focuses on non-cardiac risk factors that influence SCA risk and outcome. While cardiovascular risk factors such as heart failure and cardiac ischemia are well-known to contribute to SCA risk from several large population-based studies, non-cardiac risk factors such as non-cardiac drugs or disease are an emerging field in SCA studies, to which ARREST aims to contribute. Apart from examples from ARREST, this thesis presents several studies that examine SCA risk markers on the ECG. Part I of this thesis presents four studies based on ECG-data, whereas Part II and Part III provide an anthology of ARREST studies.

**Part I (chapters 2 – 5): Markers of SCA risk on the ECG from non-cardiac risk factors**

**Chapter 2** presents a cross-sectional, retrospective study comparing ECGs in patients with epilepsy with community-dwelling controls. In a recent community-based study, we found that people with epilepsy had a 2-3 fold increased risk of SCA. In the study presented here, we aimed to determine whether ECG-risk markers of SCA (severe QTc-prolongation, Brugada ECG-pattern, ERP) are more prevalent in people with epilepsy than in community-dwelling controls. **Chapter 3** has a similar approach in a different patient group, i.e., patients with schizophrenia. While SCA risk is increased in schizophrenia, the causes of this association are not fully resolved. In this study, we compared ECG markers of SCA-risk, in particular, Brugada-ECG pattern and QTc-prolongation, between patients with schizophrenia and community-dwelling controls. In both chapters 2 and 3, we corrected for or stratified according to medication use that might affect ECG findings. **Chapter 4 and 5** both investigate the effects of the antipsychotic drug haloperidol on the QT interval in two in-hospital populations. Haloperidol has established QT-prolonging effects on the ECG by blocking cardiac potassium channels, but its influence in patients in the presence of multiple comorbidities is less well-studied. In **chapter 4** the QT-interval before, during and after haloperidol use was measured, along with medication use and clinical variables in order to identify risk factors for potentially dangerous QT prolongation. In **chapter 5**, we explore in more detail a risk factor which we identified in chapter 4, i.e., surgery, and investigate whether effects on the ECG of haloperidol can be distinguished in a perioperative setting.

**Part II (chapters 6 – 9): Non-cardiac risk factors for SCA in the general community**

The second part of this thesis presents studies performed with data from the ARREST registry, and focuses on non-cardiac risk factors for SCA in the general community. **Chapter 6** describes the rationale and outline of the part of ARREST that was set up to study genetic, clinical and pharmacological determinants of OHCA, providing examples of possible study designs. **Chapter 7** presents a review of the cardiac sodium channel and inherited electrophysiological disorders, and provides an overview on pharmacotherapy. The cardiac sodium channel plays a pivotal role in the propagation of
electrical activity through the heart. Studying this ion channel provides valuable insights into the electrophysiological mechanisms that are at play at the level of the cardiac myocyte. Moreover, these mechanisms may be modified by non-cardiac conditions, e.g., the use of drugs prescribed for the treatment of non-cardiac disease, such as antidepressants and anti-epileptics. Chapter 8 is an example of how the combination of molecular-genetic work and patient data with a population study establishes increased SCA risk of nortriptyline, an antidepressant drug, while providing insight into the mechanism behind this increase. Chapter 9 presents a community based case-control study that investigates whether patients with obstructive pulmonary disease have an increased risk of SCA, and whether this risk is mediated by cardiovascular risk-profile and/or respiratory drug use.

**PART III: (Chapters 10 - 12): Survival after out-of-hospital cardiac arrest**

The final part of this thesis presents three population-based cohort studies investigating outcome of resuscitation attempts after OHCA, and determinants thereof. Chapter 10 presents a study that analyzes whether patients with obstructive pulmonary disease have a lower survival rate after OHCA than patients without obstructive pulmonary disease. Patient’s co-morbidities may determine survival after OHCA, and guide post-resuscitation care. Chapter 11 examines gender differences and aims to study whether access to and outcome of resuscitation attempts after OHCA differs between men and women. Finally, Chapter 12 examines whether temporal trends can be distinguished in neurologically intact survival after OHCA, and, if so, if a change in survival is attributable to increased use of the automated external defibrillator.
Chapter 1

References: