Sudden cardiac arrest: Studies on risk and outcome

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CHAPTER 6

Genetic, clinical and pharmacological determinants of out-of-hospital cardiac arrest: rationale and outline of the Amsterdam Resuscitation Studies (ARREST) registry


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Abstract

Introduction
Out-of-hospital cardiac arrest (OHCA) is a major public health problem. Recognizing the complexity of the underlying causes of OHCA in the community, we aimed to establish the clinical, pharmacological, environmental and genetic factors, and their interactions, that may cause OHCA.

Methods and analysis
We set up a large-scale prospective community-based registry (AmsteRdam Resuscitation Studies, ARREST) in which we prospectively include all resuscitation attempts from OHCA in a large study region in The Netherlands in collaboration with Emergency Medical Services. Of all OHCA victims since June 2005, we prospectively collect medical history (through hospital and general practitioner), current and previous medication use (through community pharmacy). In addition, we include DNA samples from OHCA victims with documented ventricular tachycardia/fibrillation during the resuscitation attempt since July 2007. Various study designs are employed to analyse the data of the ARREST registry, including case-control, cohort, case only, and case-cross over designs.

Ethics and Dissemination
We describe the rationale, outline and potential results of the ARREST registry. The design allows for a stable and reliable collection of multiple determinants of OHCA, whilst assuring that the patient, lay-caregiver or medical professional is not hindered in any way. Such comprehensive data collection is required to unravel the complex basis of OHCA. Results will be published in peer-reviewed journals and presented at relevant scientific symposia.
Introduction

Sudden cardiac arrest is a major health problem in the affluent world, accounting for 15–20% of all natural deaths in adults in the United States and Western Europe, and for up to 50% of all cardiovascular deaths.\(^1\) In the vast majority, it occurs in the community (out-of-hospital cardiac arrest, OHCA). It is often (up to 50%) the first sign of heart disease.\(^2,3\) Survival rates are increasing, but remain low despite intense efforts at improving treatment of OHCA victims.\(^4,6\) Prevention of OHCA is clearly desirable, and requires elucidation of the underlying disease processes and risk factors. OHCA is usually caused by cardiac arrhythmias, i.e., ventricular tachycardia/fibrillation (VT/VF). VT/VF may stem from multiple mechanisms, ultimately resulting in disrupted cardiac electrophysiology. On the level of an individual patient, multiple conditions, both inherited and acquired, interact to cause these disruptions and result in VT/VF.\(^3\)

Important predictors of OHCA, including heart failure, cardiac ischemia and diabetes, have previously been identified. However, these risk factors are often unrecognized prior to OHCA and are thus predictive in only a minority of OHCA victims. Furthermore, additional non-cardiac risk factors for OHCA (e.g., depression, epilepsy, environmental factors) have been proposed, suggesting that OHCA in the community is multi-factorial.\(^7-10\) Moreover, various drugs have been associated with OHCA, ultimately leading to their withdrawal from the market.\(^11,12\) Apparently, the strict pre-marketing safety screening systems lack the ability to identify all drugs that increase the risk of OHCA. Of note, this also applies to non-cardiac drugs, i.e., drugs prescribed for non-cardiac disease. Such drugs may cause VT/VF because they impact on cardiac electrophysiology by modulating cardiac ion channel function. Importantly, VT/VF risk from drug use often requires the added presence of other risk factors. For instance, VT/VF risk conferred by (cardiac or non-cardiac) sodium channel blocking drugs is particularly high in patients with heart failure and/or cardiac ischemia.\(^13,14\) Genetic factors may also modulate VT/VF risk. For instance, observational studies have indicated that sudden death of a family member is a risk factor for OHCA.\(^15-17\) Genetic markers for increased OHCA risk in the community have started to be found,\(^18,19\) but the role of causative genes with large effect sizes remains to be established.

Recognizing the complexity of the underlying causes of OHCA in the community, we aimed to uncover the clinical, pharmacological, environmental and genetic factors, and their interactions, that may cause OHCA. To this end, we set up a large-scale community-based registry (AmsteRdam REsuscitation STudies, ARREST) in which we prospectively include all resuscitation attempts from OHCA in a large study region in The Netherlands. Of all OHCA victims, we collect medical history, current and previous medication use, and DNA samples. The objective of this paper is to describe the design, rationale and outline of this registry, hereafter referred to as the ARREST registry.
Methods

Design and Setting

The AmsterRdam REsuscitation STudies (ARREST) is an on-going, prospective observational registry of all OHCAs in the study region North Holland, a province of the Netherlands. ARREST was set up in June 2005 to establish the determinants of outcome of OHCA.\(^{20-22}\) In July 2007, its aims were extended to include insight into the genetic, clinical, pharmacological, and environmental determinants of OHCA in the community.\(^{10,18,19}\) To minimize selection bias, data of all resuscitation attempts with involvement of emergency medical services (EMS) in the study region are collected and stored in the ARREST database. The study region covers 2404 km\(^2\) (urban and rural communities) and has a population of 2.4 million people. All studies with the ARREST registry are conducted according to the principles expressed in the Declaration of Helsinki. Since OHCA is an emergency situation, consent cannot be asked before data collection. From all participants who survive OHCA, written informed consent for collection and use of medical and pharmacological information and DNA samples is obtained after discharge from the hospital. The Ethics Committee of the Academic Medical Center, a teaching hospital in Amsterdam, approved the study protocol, and the use of data from patients who did not survive OHCA, and of data needed to evaluate the outcome of the resuscitation attempt.

**EMS system in the study region**

In a medical emergency, people dial the national emergency number. When the EMS dispatcher suspects OHCA, he/she dispatches two ambulances. Ambulance personnel are equipped with a manual defibrillator and qualified to perform Advanced Life Support. In part of the study area, the EMS dispatcher also sends out first responders (firefighters or police officers) equipped with an automated external defibrillator (AED) in the event of a suspected OHCA. In addition, the placements of AEDs in public areas has been facilitated by public and private initiatives during the study period, but is not centrally controlled or directed.\(^{20}\) All four EMS services in the study region participate in ARREST.

**Data collection**

Resuscitation parameters

After each resuscitation attempt, EMS paramedics routinely send the continuous ECG and impedance recordings from their manual defibrillators to the study center by modem. When an AED is used prior to EMS arrival, ARREST study personnel visits the AED site shortly after the OHCA, and collects the AED ECG recording. All ECGs are stored and analyzed with dedicated software (Code Stat Reviewer 7.0, Physio Control, Redmond WA, USA), allowing for analysis of heart rhythm/arrhythmia during the resuscitation
attempt. Data items concerning the resuscitation procedure are collected according to the Utstein recommendations. Ambulance personnel is obliged by protocol to call the study center after every OHCA to provide additional information on the resuscitation (e.g., whether OHCA was witnessed, whether basic life support was provided before arrival of ambulance personnel, whether the patient died at the resuscitation site or was transported to a hospital). Hospital files are reviewed by ARREST study personnel to retrieve data of in-hospital resuscitation care / treatment (i.e. therapeutic hypothermia, angiography), outcome and neurological status when discharged alive.

OHCA is defined as the out-of-hospital occurrence of cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation. All arrests are deemed to result from cardiac causes unless an unequivocal non-cardiac cause (i.e., trauma, drowning, intoxication) is documented. All EMS and hospital case files are reviewed to verify the presence or absence of a non-cardiac cause. In addition, data items concerning medication use and medical history are collected. For the sake of DNA discovery studies, the best possible ascertainment of a cardiac cause of OHCA is achieved by collecting DNA samples only of patients with documented VT/VF at any time during resuscitation. Patients in whom only asystole (but no VT/VF) is recorded, are excluded, as asystole is the end stage of any cardiac arrest, and may be due to non-cardiac causes.

DNA samples
In order to avoid interventions during the resuscitation attempt for research purposes only, DNA samples are collected as follows. Of patients who die on the scene and are not transported to the hospital, DNA is extracted from the endotracheal tube placed for ventilation during the resuscitation attempt (no blood is usually drawn before hospital admission). Endotracheal tubes are collected at ambulance posts or emergency rooms by study personnel. Of patients who reach the hospital alive, DNA is extracted from blood lymphocytes of blood that is routinely collected and analysed in the hospital’s lab for patient care. Unused blood (available in >95% of the patients) is sent to the ARREST study center or collected by study personnel, and is used for DNA analysis and to determine metabolic parameters.

If future analyses of the collected DNA material reveal pathogenic mutations that require medical action, the patient is contacted through his/her general practitioner (GP) and the patient has indicated that he/she wishes to be informed when giving informed consent. Genetic counseling is offered to the patient and the patient’s relatives in such a case.

Medical information
Medical information (medical history including mental health, current disease diagnosis, survival status and, if applicable and available, post mortem examination) is collected by
contacting the hospital of admission, and the patient’s GP, and conducting telephone interviews with surviving patients. In the Netherlands, every citizen has a GP who acts as gatekeeper for all medical care. GP records contain information on diagnoses from GPs/specialists that are based on guidelines for GPs/specialists. Diagnoses in the GP files are recorded according to the International Classification of Primary Care (ICPC) system. The GPs are asked to mark in a questionnaire whether their patient was diagnosed prior to their OHCA with any medical condition. In addition, GPs are asked to send all medical correspondence with all treating medical specialists to the ARREST study center.

Pharmacological information

Information regarding medication use (current medication at the time of OHCA and in the year before OHCA) is obtained by contacting the patient’s community pharmacist. Exposure to medication is determined by reviewing dispensing information prior to the date of OHCA. Dosage and duration of medication use is recorded of all medication use and used to calculate the time during which a patient is exposed.

Environmental information

To assess the influence of environmental factors on OHCA risk, we analyse the socioeconomic and environmental characteristics of the patient’s place of residency. Such data on a neighbourhood level are available from Statistics Netherlands, a Dutch governmental institution.

Data analysis

Data and DNA material collected by the ARREST registry can be analysed using various study designs.

We employ case-control designs, collaborating with registries and studies that provide suitable controls for ARREST OHCA-cases. Cases are matched to controls according to age, sex and OHCA date. Controls are drawn from a registry that contains drug dispensing records from community pharmacies (PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands. Available from: http://www.pharmo.nl/), and from a database that contains the complete medical records of >60,000 people from a large group of GPs in the study area (HAG-net-AMC). Genetic data of ARREST OHCA-cases are compared to data registries with DNA samples of normal control populations.

In a cohort study, we compare a group of ARREST OHCA-cases with a particular property to a group of cases without that property. For example, we study ARREST OHCA-cases with and without obstructive pulmonary disease, and compare their survival to hospital discharge.
Figure 1: Patient inclusion in the year 2009.
**Case only designs** are employed when studying effects of interactions on OHCA risk, e.g., between a particular gene profile and exposure to study drugs; in this way, we test the hypothesis that certain gene profiles may modify the risk of the study drug on OHCA.27

In a *case cross-over* design, properties of the ARREST OHCA-case (e.g., exposure to study drug) are compared with the same property at an earlier time point (e.g., 6 months before OHCA), thereby reducing confounding and selection bias.

**Results**

Data collection of resuscitation parameters started in June 2005. In July 2007, we started collecting DNA samples. Each year, we collect data from ~1000 resuscitation attempts, ~50% of which have VT/VF documentation. Figure 1 shows the inclusion scheme of all VT/VF cases that we have included in the year 2009, the first year in which all hospitals and ambulance services participated in DNA collection. In this one-year period, we registered 1162 resuscitation attempts, of which 871 had a cardiac cause without EMS witness. In 498 cases, VT/VF was documented. Of these VT/VF cases, 23% (114) died on the scene, 24% (121) died in the emergency room before hospital admission, while 53% (263) were admitted to the hospital. DNA samples were collected in 60% of cases who died on the scene, in 83% of cases who died in the emergency room and in 94% of cases who were admitted to the hospital.

Table 1 presents medication data per indication category of ARREST OHCA-cases (N=1787, mean age 66.5, 77% male) collected in the period 2005-2009, and age/sex/OHCA date-matched non-OHCA controls from the PHARMO database (N=7698). As expected, medication use for cardiovascular diseases was higher among cases than controls. Drugs used for several other categories were also more prevalent among cases, inviting further research.

Figure 2 shows the inclusion rate of DNA samples in the period July 2007-January 2014. We included 3005 cases, and continue to collect DNA samples at the same rate. The average yield of DNA from blood samples was 160 μg DNA, while tubes yielded 6.9 μg DNA. Inclusion rate was stable over the past years.

**Discussion**

The pathophysiology of OHCA is extremely complex, and its causes are highly heterogeneous. In many patients, it is not possible to single out one individual cause. Instead, cardiac arrest results from various interacting causes and circumstances and a final trigger. This complicates community-based research into the etiology of OHCA to an enormous extent. Furthermore, since OHCA occurs in such an unpredictable
manner, it is difficult to obtain consent, precise data on circumstances of OHCA and, most notably, DNA samples. To increase the chances for discovery of relevant DNA profiles, ascertainment of a cardiac cause of OHCA is crucial. To this end, we chose to define a clear and unambiguous selection criterion: documented VT/VF. We expect that with this precise case definition, we will create a more homogeneous cohort of OHCA cases for analysis, thereby increasing our ability to identify genetic risk factors. Our close collaboration with EMS services in the study region enables us to include all OHCA cases in the study region, thereby enabling us to also compare patients with or without VT/VF. Our study design thus allows us to study the full range of clinical, pharmacological, environmental and genetic risk factors of OHCA, and their interactions.

Table 1: Medication use (ATC Classification system categories) of OHCA cases and age/sex-matched controls

<table>
<thead>
<tr>
<th>Category</th>
<th>ARREST OHCA with documented VT/VF</th>
<th>PHARMO controls</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>1787</td>
<td>7698</td>
</tr>
<tr>
<td>Male sex</td>
<td>1376 (77.0)</td>
<td>5939 (77.1)</td>
</tr>
<tr>
<td>Mean age (standard deviation), years</td>
<td>66.5 (13.7)</td>
<td>66.4 (13.8)</td>
</tr>
<tr>
<td>A - Alimentary tract and metabolism</td>
<td>810 (45.3)</td>
<td>2607 (33.9)</td>
</tr>
<tr>
<td>B - Blood and blood forming organs</td>
<td>925 (51.8)</td>
<td>2401 (31.2)</td>
</tr>
<tr>
<td>C - Cardiovascular system</td>
<td>1268 (71.0)</td>
<td>3903 (50.7)</td>
</tr>
<tr>
<td>G – Genito Urinary system and sex hormones</td>
<td>221 (12.4)</td>
<td>911 (11.8)</td>
</tr>
<tr>
<td>H – Systemic hormonal preparations, excluding sex hormones</td>
<td>181 (10.1)</td>
<td>563 (7.3)</td>
</tr>
<tr>
<td>J – Anti-infectives for systemic use</td>
<td>410 (22.9)</td>
<td>1416 (18.4)</td>
</tr>
<tr>
<td>L – Antineoplastic and immunomodulating agents</td>
<td>53 (3.0)</td>
<td>177 (2.3)</td>
</tr>
<tr>
<td>M – Musculo-skeletal system</td>
<td>354 (19.8)</td>
<td>1420 (18.4)</td>
</tr>
<tr>
<td>N – Nervous system</td>
<td>557 (31.2)</td>
<td>1966 (25.5)</td>
</tr>
<tr>
<td>P – Antiparasitic products, insecticides and repellents</td>
<td>12 (0.7)</td>
<td>73 (0.9)</td>
</tr>
<tr>
<td>R – Respiratory system</td>
<td>426 (23.8)</td>
<td>1524 (19.8)</td>
</tr>
</tbody>
</table>

Data are N (%), unless otherwise indicated. ATC, Anatomical Therapeutic Chemical (ATC) Classification System; OHCA, out-of-hospital cardiac arrest; SD, standard deviation; VF, ventricular fibration; VT, ventricular tachycardia.
Figure 2: Collection of DNA samples of OHCA victims with VT/VF July 2007-January 2014

DNA sample inclusion until January 2014 (N=3005)

Of added importance, our study group has the ability to complement findings from these association studies with mechanistic studies in the experimental laboratory. This laboratory is equipped with a comprehensive range of experimental techniques, including molecular biology, molecular genetics, single-cell electrophysiology (patch-clamp studies), and tissue, organ, and *in vivo* electrophysiology. Moreover, our study group is also embedded in the cardiology and cardiogenetics departments. This organization in which these various domains are interwoven offers the possibility that research questions from one domain feed into the other domains. This allows for a multifaceted approach to resolve the causes of OHCA in the community.28

Finally, the ARREST infrastructure is not only suitable to study the causes of OHCA, but also its outcome. The fact that data regarding the resuscitation attempt are collected according to Utstein recommendations enables us to study survival at the various stages of post-resuscitation care. This allows for evaluation of the effects of various interventions in the chain-of-survival care after OHCA.
Conclusion

We describe the rationale, outline and potential results of the ARREST database. To our knowledge, ARREST is the first prospective population-based registry of patients with OHCA aimed at identifying genetic, clinical, pharmacological and environmental determinants of OHCA with documented VT/VF. The data presented here show that our study design allows for a stable and reliable registry of OHCA.

Author’s contributions

MTB, AB, JB, PCS, RWK, AdB and HLT conceived the study. RWK and HLT obtained funding for the study and supervise it. MTB, DvH, AB and JB collected data. MTB, DvH, AB, JB and HLT wrote the manuscript. PCA, MLdB, RWK and AdB provided critical revisions of the manuscript.

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Competing interests statement.

The authors declare there are no conflicts of interest.
References


