New technologies and decision making in out-of-hospital cardiac arrest

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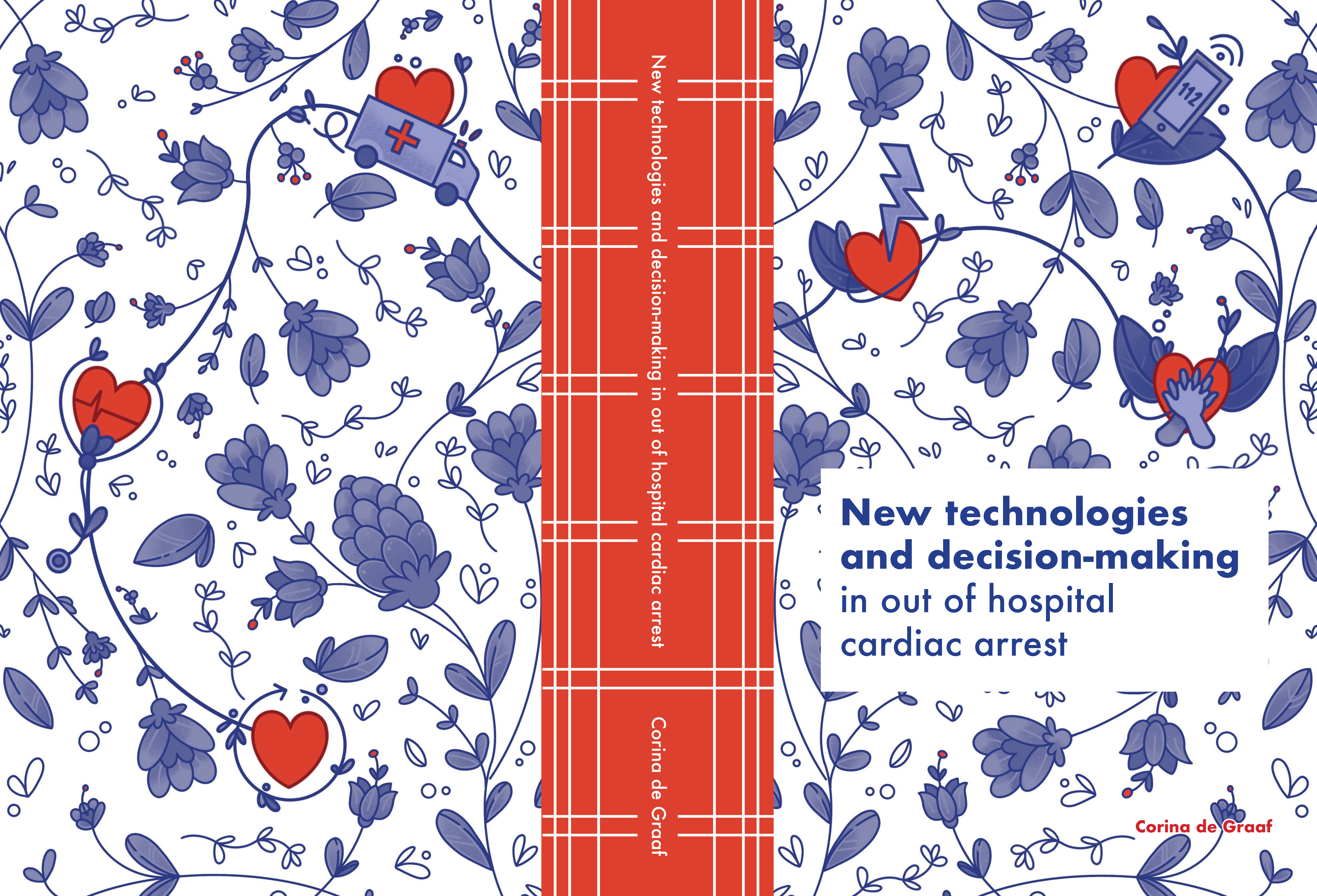

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New technologies and decision making in out-of-hospital cardiac arrest

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CHAPTER 1

1

General introduction and outline of thesis

General introduction

The outcome of out-of-hospital cardiac arrest (OHCA) patients depends on multiple elements during the resuscitation process. A shockable initial rhythm is one of the most important predictors.[1] Patients with a shockable rhythm are more likely to survive when help is provided as early as possible. The 'Chain of Survival' summarizes the elements needed for successful resuscitation. (Figure 1). The chain consists of four links: early recognition and call for help, early cardiopulmonary resuscitation (CPR), early defibrillation (in case of a shockable rhythm), and post-resuscitation care.[2]

Figure 1. Chain of survival

Organization of EMS in the Netherlands

In case of a medical emergency, the national emergency number will be dialed and if the dispatcher suspects an OHCA, two Emergency Medical Services (EMS) teams are dispatched. Each team consists of a driver, who is qualified to perform basic life support (BLS), and a paramedic, who is qualified to perform advanced life support (ALS). Simultaneously with EMS, first responders are dispatched, equipped with an automated external defibrillator (AED). These first responders are firefighters and police officers trained in BLS and AED use. Dispatchers also alert citizen-responders who use AEDs placed in public areas in the study region. Anyone in the study region is allowed to use these AEDs. The EMS follow a national protocol for cardiac arrest based on the European guidelines.[3] The EMS paramedics are qualified and legally allowed to make decisions on termination of resuscitation in the prehospital setting without consulting a physician.

Shockable initial rhythm

Patients with a shockable initial rhythm (ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT)) are more likely to survive if they receive early CPR and early defibrillation (figure 2).[4-10] Currently, about 25-50% of patients have VF, however, this percentage has declined from proportions as high as 70% over the years worldwide.[11-15] This decline may be caused by a lower occurrence of VF at initial collapse.[13] Another explanation for the decline could be a longer delay to the first electrocardiographic (ECG) recording. As the time from collapse passes, VF will deteriorate into asystole and thereby decreasing survival chances.[16] For OHCAs occurring at a residential location such a delay is generally longer (e.g. caused by longer response intervals and/or lower rates of witnessed collapse) compared to those occurring at a public location [17,18] Besides a longer delay, OHCA patients at a residential location are older and have more comorbidities which may result in a lower rate of VF.[19] Taking this and the overall observed decline in proportion VF into account, the question has arisen if it is worthwhile for OHCA patients at a residential location to be involved in public access defibrillation initiatives with AEDs.[20]

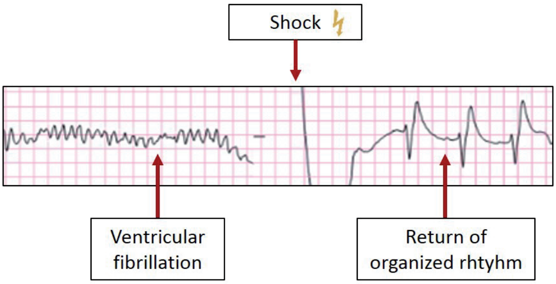

Figure 2. Ventricular fibrillation and delivery of a defibrillation shock resulting in return of organized rhythm

The use of an AED and first responder systems

Defibrillation is increasingly performed by bystanders and dispatched first responders (police, firefighters, or citizen-responders) using AEDs before the arrival of Emergency Medical Services (EMS).[4-7] The use of an AED before the arrival of EMS reduces the time from call to defibrillation of OHCA patients with a shockable initial rhythm and therefore increases the survival chances of patients with a shockable initial rhythm.[8-10] To increase the likelihood of early CPR and early defibrillation with an AED, systems that dispatch first responders have been developed all over Europe.[21-23] Between European regions, survival rates after OHCA vary widely.[24] The presence or absence of a dispatched first responder system could be one of the factors which contribute to this variation.

Transfer of AED information

If an AED is used before the arrival of EMS, EMS personnel may not be aware that a shockable rhythm had been present. Early defibrillation by an AED could restore the heart rhythm before EMS arrives at the scene and the patient may not require further EMS shocks.[25] The transfer of the information on the initial rhythm (or delivery of an AED shock) depends on an oral account of the person who connected and used the AED to EMS personnel and subsequently to the physician in the treating hospital. In the hectic emergency setting of an OHCA and emergency department, the accurate transfer of this vital information could be hampered.[26] Also, AED users may be unaware of the importance of this information for the diagnosis and clinical decision-making during post-resuscitation care and do not transfer information on the presence of a shockable rhythm to EMS personnel.[27] So, increased AED use may contradictory result in incorrect information on the presence of a shockable rhythm.

AED instructions and new technologies

The standard settings of AEDs use voice prompts that instruct the user to interrupt chest compressions for heart rhythm analysis every two minutes (figure 3).[28,29]

Figure 3. European Resuscitation Council Guidelines instruction: interrupt chest compressions and clear patient for AED analysis

This programmed interruption for rhythm analysis, although necessary, results in interruptions of chest compressions and long pre-shock pauses which are an important undesired consequence of the AED algorithm and negatively influence survival.[30,31] An AED algorithm that can analyze the heart rhythm during chest compressions could result in decreased hands-off time and benefit the patient. However, the diagnostic performance and clinical value of such an algorithm incorporated in an AED used in the daily practice of actual cardiac arrest have not been investigated and was identified as an important knowledge gap in the Science on Cardiopulmonary Resuscitation.[32]

Advanced life support and return of spontaneous circulation

The moment EMS paramedics arrive at the scene of an OHCA they will immediately start with advanced life support (ALS) to achieve the return of spontaneous circulation (ROSC). The resuscitation on scene ends when a patient is either transported to the hospital emergency department or when the resuscitation is terminated on scene.[3] In only 10% to 50% of OHCA patients ALS results in ROSC on scene.[33-36] At the start of resuscitation it is not known if and when a patient achieves ROSC. The current guidelines recommend applying termination of resuscitation (TOR) rules to specific groups of patients after EMS arrived on scene, but do not describe the optimal time on scene until the decision to transport in patients without ROSC.[3,37] The termination of resuscitation guidelines apply to approximately 30% of patients with OHCA, however many patients that do not meet these criteria, do not achieve ROSC on scene.[38,39]

Transport to the hospital without ROSC

The survival of OHCA patients transported to the hospital without ROSC is, although low, above a 1% futility rate.[40-43] The transport of patients with ongoing CPR may reduce the quality of CPR but can be potentially beneficial if treatment options can be applied that are generally unavailable in the pre-hospital setting. There is evidence that extracorporeal cardiopulmonary resuscitation (ECPR) could be a beneficial treatment option, although the precise indications and its limitations are not yet well defined.[44-46] Little is known about the optimal duration of resuscitation on scene and when transport should be initiated in patients without ROSC.[47] EMS have to consider the risk of transporting an unstable patient in a moving vehicle who may have achieved ROSC if resuscitation efforts had continued longer on scene. Currently, it is unclear at what time in the resuscitation process the decision to transport should be made during ongoing CPR.

Factors that influence the decision making on scene

The decision to terminate or transport a patient without ROSC may be influenced by other factors than guidelines. Factors as compromised scene safety, the expectation of the public, and environmental circumstances could influence the decision to start transport with ongoing CPR. [48-50] It is rarely documented which factors contribute to the EMS decision to transport or terminate resuscitation on scene in patients without ROSC. A better understanding of these factors might offer the opportunity for targeted interventions for better decision-making on scene.

Amsterdam Resuscitation Studies (ARREST)

The ARREST study is an ongoing and long-lasting prospective registry of all-cause OHCA in the province North-Holland (excluding Gooi-en Vechtstreek) of the Netherlands. The data used in all studies described in this thesis were derived from the ARREST registry.

Aim and outline of this thesis

The studies presented in this thesis aim to address the issues outlined in the above introduction. In part one we describe the occurrence of shockable initial rhythm over time. In **chapter 2** we study the proportion of shockable initial rhythm and whether it is still declining over a 10-year time period across multiple emergency medical services (EMS) in four different European countries. Furthermore, we describe whether there is a difference in the decline of shockable initial rhythm between OHCAs occurring at a residential location and those at public locations.

In part two we describe the contribution of systems dispatching first responders in Europe, the transfer of AED information to treating physicians, and the implementation of new AED technology. In **chapter 3** we study whether the presence of a system dispatching first responders (firefighters, police officers, and citizen responders) with AEDs may lead to higher survival rates in European regions. In **chapter 4** we describe how often a shockable heart rhythm was stored only in an AED and in such situations, how often the fact that a shockable rhythm had been present as a cause of the OHCA was known to the treating physicians at the hospital. In **chapter 5** we examine a new AED algorithm that is able to analyze the heart rhythm during chest compressions and assess the clinical value of the algorithm compared to a conventional AED algorithm.

In part three we describe OHCA patients transported without ROSC, the optimal duration of resuscitation before the start of transport, and factors influencing the decision to transport or to terminate resuscitation on-site. In **chapter 6** we investigate the association between the duration of resuscitation on scene and survival in patients transported with ongoing CPR. In **chapter 7** we assess the rate and time of prehospital ROSC and 30-day survival and investigate the optimal timing of the decision to initiate transport without ROSC. In **chapter 8** we explore medical and nonmedical factors that contribute to the decision to transport or terminate the resuscitation on scene and assess the differences between patients without ROSC transported to the hospital and patients where the resuscitation is terminated on scene.

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PART 1

Occurrence of shockable initial rhythm

CHAPTER 2

2

Occurrence of shockable rhythm in out-of-hospital cardiac arrest over time: A report from the COSTA group

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Abstract

Background

Prior research suggests that the proportion of a shockable initial rhythm (SIR) in out-of-hospital cardiac arrest (OHCA) declined during the last decades. This study aims to investigate if this decline is still ongoing and explore the relationship between location of OHCA and proportion of a SIR as initial rhythm.

Methods

We calculated the proportion of patients with a SIR between 2006-2015 using pooled data from the COSTA-group (Copenhagen, Oslo, Stockholm, Amsterdam). Analyses were stratified according to location of OHCA (residential vs. public).

Results

A total of 19,054 OHCA cases were included. Overall, the total proportion of cases with a SIR decreased from 42% to 37% (P<0.01) from 2006 to 2015. When stratified according to location, the proportion of cases with a SIR decreased for OHCAs at a residential location (34% to 27%; P=0.03), while the proportion of a SIR was stable among OHCAs in public locations (59% to 57%; P=0.2). During the last years of the study period (2011-2015), the overall proportion of a SIR remained stable (38% to 37%; P=0.45); this was observed for both residential and public OHCA.

Conclusion

We found a decline in the proportion of patients with a SIR in OHCAs at a residential location; this decline levelled off during the second half of the study period (2011-2015). In public locations, we observed no decline in SIR over time.

Introduction

A shockable initial rhythm (SIR) is one of the most important predictors of survival after an out-of-hospital cardiac arrest (OHCA). Patients with a SIR are more likely to survive if they are quickly defibrillated.[1] However, multiple reports suggest that the proportion of SIR in OHCA has declined worldwide and rates of SIR as low as 24% have been reported.[2-6]

A decline in proportion of SIR may be caused by lower occurrence of a SIR at initial collapse, which has been suggested by prior research.[4] Another explanation of lower observed rates of SIR is longer delays to first electrocardiographic (ECG) recording. As time from collapse passes, SIR will eventually degenerate into asystole. Thus, patients presenting in asystole may have actually had a SIR at the time of the collapse. Such a delay (e.g. caused by longer response intervals and/or lower rates of witnessed collapse) is generally longer in OHCAs occurring at a residential location, as opposed to those occurring in a public location.[7,8] In addition, OHCA patients at a residential location are older and have more comorbidities that may result in lower rate of a SIR.[9] Because these OHCA patients may also face the abovementioned decline in proportion of a SIR, the question has arisen whether public access defibrillation initiatives to involve automated external defibrillators (AED) in the resuscitation effort are worthwhile for OHCA patients at a residential location.[10]

Therefore, it is important to study whether the decline in proportion of SIR is continuing. This study aims to determine whether the proportion of SIR is still declining over a 10-year time period up to 2016 across multiple emergency medical services (EMS) in four different European countries. Secondly, this study aims to determine whether this decline in proportion of SIR is different between OHCAs occurring at a residential location and those at public locations.

Methods

COSTA group

The COSTA group is a collaboration network of resuscitation researchers in Copenhagen (Denmark), Oslo (Norway), Stockholm (Sweden), and Amsterdam (the Netherlands), which aims at joining research efforts in OHCA and early defibrillation. Data from OHCA events across all COSTA sites were merged and analyzed in a central research database within the COSTA collaboration. This study was performed in line with the Helsinki declaration.[11] Ethical approval was granted by the ethical boards for each study site.

Setting, study regions and emergency medical service systems

Denmark: central Copenhagen

Central Copenhagen covers 97 km^2 and holds approximately 680,000 inhabitants. Incidence of OHCA was 81 cases per 100.000 in 2014. The EMS of Copenhagen is a two-tiered system comprising ambulances equipped with defibrillators providing basic life support (BLS) and physician-staffed mobile emergency care units providing advanced life support (ALS). OHCA patients with an EMS resuscitation attempt are included in the registry. Also, OHCA patients with AED defibrillation by bystanders only (either with or without return of spontaneous circulation (ROSC) at arrival of the ambulance) are included in this registry. If already deceased, OHCA patients are not included in the registry. Only physicians can decide to terminate a resuscitation effort.

Norway: Oslo

Before 2009, Oslo EMS covered a population of approximately 550,000 inhabitants in 454 km^2, and was served with one-tiered ambulance service manned with paramedics and emergency medical technicians. Incidence of OHCA was 57 cases per 100.000 in 2014. After 2013, Oslo and Akershus EMS were merged to serve a population of approximately 1.2 million inhabitants in a mixed urban and rural area of 5371 km^2. Before 2013, OHCA patients were included if treatment by ambulance (either CPR for at least 30 seconds or defibrillation) was started. After 2013 the inclusion criteria changed to: treatment by either bystanders, first responders, or ambulance. Patients already deceased were not included in the registry. Paramedics may decide to terminate the resuscitation effort without consulting a physician, and declare death. OHCA patients with AED defibrillation only and ROSC at arrival of the ambulance were not included in the registry in the study period.

Sweden: Stockholm region

Stockholm region covers 6519 km^2 and has 2.1 million inhabitants. Incidence of OHCA was 38 cases per 100.000 per year in 2014. There is a two-tiered EMS system in Sweden for responses to all medical emergencies. Both tiers consist of EMS units with registered nurses in prehospital care providing ALS and with AED or manual defibrillation. All OHCA patients treated with CPR and/or defibrillation initiated by bystanders, first responders or EMS as well as OHCA patients with AED defibrillation only and ROSC at arrival of the ambulance are included in this registry. If already deceased, OHCA patients are not included in the registry. Paramedics may decide to terminate the resuscitation effort without consulting a physician, and declare death.

The Netherlands: province of North Holland

The province of North Holland covers 2404 km^2 and has 2.4 million inhabitants. Incidence of OHCA was 46 cases per 100.000 in 2014. In response to an OHCA, two ambulances of a single tier are dispatched. Ambulance personnel are equipped with manual defibrillators and perform ALS. OHCA patients with AED defibrillation by bystanders or first responders only and ROSC at arrival of the ambulance are also included in this registry. If already deceased, OHCA patients are not included in the registry. Paramedics may decide to terminate the resuscitation effort without consulting a physician. If so, a physician comes to the scene to declare death. Also, OHCA patients are included in the registry only if they have been resuscitated by the EMS for >2 minutes.

Study question, study population and data collection

The primary purpose of this paper was to determine whether the proportion of SIR changed during the study period, and whether this differed between OHCAs occurring at a residential or public location. We included patients in whom EMS personnel attempted resuscitation for OHCA between January 1, 2006 and December 31, 2015. We excluded patients with obvious non-cardiac cause of the arrest and EMS-witnessed OHCAs. All registries used the Utstein template for data reporting.[12] For the Oslo region, only data from 2006-2008 and 2012-2015 were included, while for the Copenhagen region, only data from 2008-2015 were included, for reasons of availability. All data were anonymized and pooled into a central COSTA database.

Definitions

The initial rhythm recorded by EMS manual defibrillator or AED (whichever was first) was categorized as shockable (ventricular tachycardia, ventricular fibrillation or shock by an AED) or non-shockable (asystole, pulseless electrical activity). Outcome was defined as proportion of SIR rather than incidence of SIR, in order to attenuate effects of registry differences. Location of collapse was retrieved from EMS-call or dispatch form. All non-residential locations were considered public. Long term care facilities were classified as residential location. Time to EMS-arrival was defined as the difference between the time of the EMS-call to the dispatch centre and the time of vehicle stop of the first ambulance, except for the Copenhagen region: here, time to EMS-arrival was defined as the differences between time of dispatch of the first ambulance and time of vehicle stop. Defibrillator connection time was defined as the time interval between EMS-call and connection of the defibrillator device to the patient (EMS manual defibrillator or AED, whichever came first; North Holland region only). Other resuscitation characteristics included were witnessed collapse, bystander CPR and defibrillation by AED.

Data analysis

Proportions of SIR, using the pooled COSTA database, were calculated for each study year (2006-2015), as well as for each study region separately. Categorical variables were presented as percentages and continuous variables as mean and standard deviation (SD) or as median and interquartile range (IQR) depending on the data distributions. To compare categorical data, the trend in time was tested using chi-square statistics. To

compare continuous data, the trend in time was tested using the Jonckheere-Terpstra test. To determine whether trends were consistent during the study period, we separately analyzed the study years 2006-2010 (Period 1) and 2011-2015 (Period 2). In addition, analyses were stratified according to OHCA location.
Since the included OHCA cases originated from four different study regions, we performed a multilevel analysis to account for region effects. Furthermore, time trends in proportion of SIR were tested using regression analysis while adjusting for study region and/or resuscitation characterics where applicable.
Finally, proportions of SIR were analyzed in relation to defibrillator connection time. All statistical tests were two-tailed, and a P-value of <0.05 was considered to be statistically significant. Statistics were performed in SPSS 24 (IBM Corporation, Armonk, NY).

Results

A total of 19,054 EMS-treated OHCA patients were included for analysis (Table 1), of which 13,181 (69%) occurred at a residential location (eTable 1) and 5834 (31%) in a public location (eTable 1). Baseline characteristics per study region are provided in eTable 2 to 5.

Demographic and resuscitation characteristics

Median age increased from 69-70 years (*P* for trend <0.01). Patients were more often male, proportions varying between 68% to 73% (*P* for trend=0.44) (Table 1). The proportion of witnessed collapse decreased from 74% to 65% (*P* for trend <0.01). The proportion of bystander CPR increased from 56% to 74% (*P* for trend <0.01), as well as the proportion of AED defibrillation which increased from 9% to 21% (*P* for trend <0.01) (Figure 1A, Table 1). The proportion of OHCAs occurring at public locations (Figure 1A) did not change over time (Table 1). Stratification according to location showed that similar trends were observed for both OHCAs occurring at residential (Figure 1B, Table 2) and in public locations (Figure 1C, Table 3). Both in public and residential locations, bystander CPR increased (public 69% to 86%, residential: 50% to 69%, both *P* for trend <0.01), as did AED defibrillation (public 13% to 35%, residential: 7% to 14%, both *P* for trend <0.01).

Proportion of shockable initial rhythm

During the total study period the proportion of SIR decreased from 42% to 37% (*P*<0.01) (Figure 2A). When stratified according to OHCA location, the proportion of SIR decreased statistically significant for OHCAs at a residential location (34% to 27%; *P*<0.01) (Figure 2B), but not for OHCAs in a public location (59% to 57%; *P*=0.24) (Figure 2C).

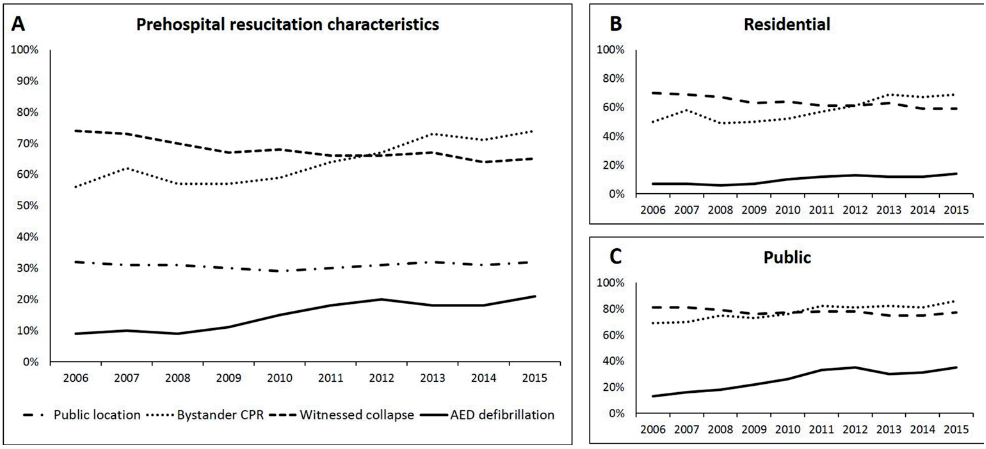

Figure 1. resuscitation characteristics.

A: Prehospital resuscitation characteristics per year in total; **B:** Prehospital resuscitation characteristics per year at residential location; **C:** Prehospital resuscitation characteristics per year in public**.** Abbreviations: AED, Automated external defibrillator; CPR, cardiopulmonary resuscitation.

Multilevel analysis indicated that study region did not affect the slope of the association between study year and proportion of SIR (P<0.05). Accordingly, adding 'region' to a logistic regression with study year as determinant of SIR did not meaningfully affect the odds ratio (OR) of study year ($OR_{unadjusted}$ study year = 1.019, p<0.001; $OR_{adjusted}$ study year = 1.016, p=0.003). During Period 1, the total proportion of SIR declined (42% to 37%; *P*<0.01) (Figure 2A). The proportion of SIR for OHCA at a residential location also declined (34% to 28%; *P*=0.03) (Figure 2B), but remained stable for OHCA in a public location (59% to 60%; *P*=0.53) (Figure 2C). However, during Period 2, there was no decrease in proportion of SIR, neither overall (38% to 37%; *P*=0.45) (Figure 1A), nor when stratified according to location (residential: 30% to 27%; *P*=0.40; public location: 59% to 58%; *P*=0.50 [Figure 2B, 2C]).

To further explore a possible explanation of the stabilized proportion of SIR in the residential location, we separately analyzed resuscitation characteristics in Period 1 and Period 2. During Period 1 we observed a decrease in witnessed status (*P*<0.01) but proportion of bystander CPR (*P*=0.33) remained stable. During Period 2, we observed a stable proportion of witnessed status (*P*=0.17) but the proportion of bystander CPR increased (*P*<0.01) (eTable 6). However, adding bystander CPR to a logistic regression with year as determinant of SIR did not meaningfully affect the OR of study year ($OR_{unadjusted}$ study year = 1.001, *P*=0.944; $OR_{adjusted}$ study year = 1.017, *P*=0.386).

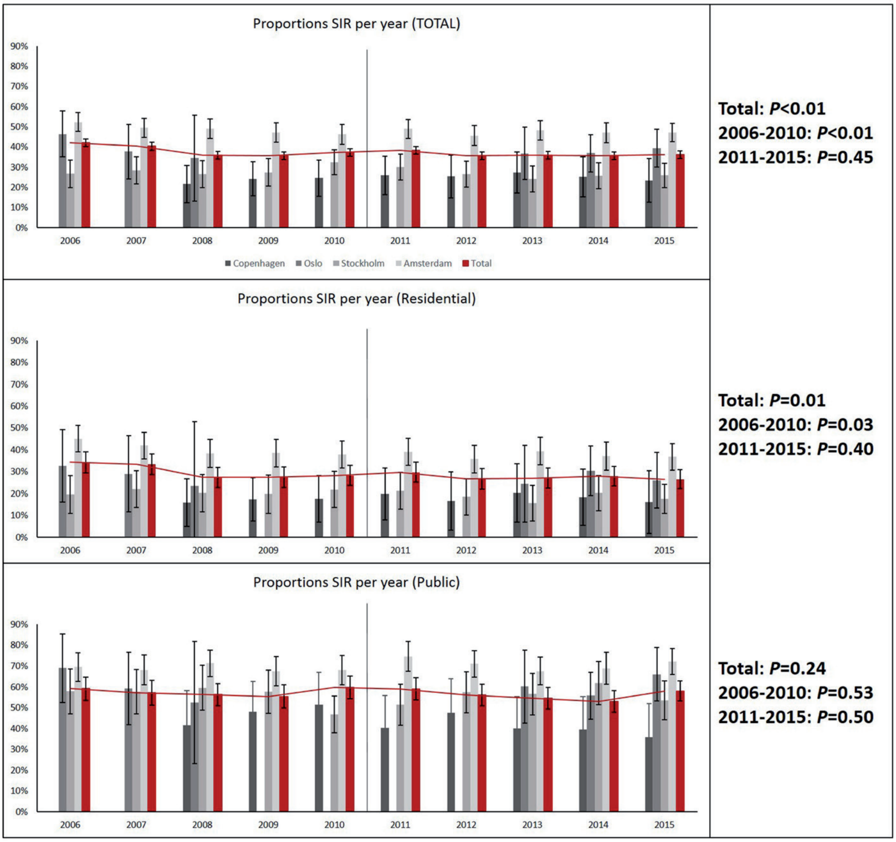

Figure 2. Proportions of shockable initial rhythm from 2006-2015

A: Proportions shockable initial rhythm per year in total; and per region; **B:** Proportions shockable initial rhythm per year at residential location; and per region; **C:** Proportions shockable initial rhythm per year in public; and per region. Abbreviations: SIR, shockable initial rhythm

Table 1. Baseline and resuscitation characteristics of OHCA patients with presumed cardiac cause

Baseline characteristics	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	*P* for trend	Missing n (%)
Patients, n	1611	1631	1916	1884	1920	1852	1811	2042	2155	2332		
Copenhagen, n	NR	NR	352	414	362	315	256	271	286	252		
Oslo, n	158	130	56*	NR	NR	NR	NR	144**	287	263		
Stockholm, n	602	624	635	601	672	640	685	725	706	746		
North Holland, n	851	877	873	869	886	897	870	902	876	971		
Age***	69 (58, 79)	69 (58, 79)	68 (58, 79)	69 (59, 80)	70 (59, 80)	69 (58, 80)	69 (60, 80)	69 (60, 80)	70 (58, 80)	70 (60, 79)	<0.01	201 (1%)
Male sex[†]	1175 (73%)	1131 (69%)	1336 (70%)	1305 (69%)	1312 (69%)	1274 (69%)	1230 (68%)	1432 (70%)	1502 (70%)	1562 (70%)	0.44	42 (<1%)
Public location[†]	508 (32%)	498 (31%)	595 (31%)	560 (30%)	555 (29%)	550 (30%)	553 (31%)	652 (32%)	664 (31%)	699 (32%)	0.54	39 (<1%)
Bystander CPR[†]	897 (56%)	999 (62%)	1060 (57%)	1056 (57%)	1112 (59%)	1177 (64%)	1194 (67%)	1484 (73%)	1520 (71%)	1645 (74%)	<0.01	235 (1%)
Witnessed collapse[†]	1181 (74%)	1175 (73%)	1320 (70%)	1242 (67%)	1274 (68%)	1189 (66%)	1176 (66%)	1333 (67%)	1360 (64%)	1426 (65%)	<0.01	284 (1,5%)
Time call to scene arrival***[‡]	9 (7,12)	10 (7,13)	8 (6,12)	8 (6,12)	9 (6,12)	8 (6,11)	8 (6,12)	9 (6,12)	9 (6,12)	8 (6,11)	<0.01	2188 (11%)
Initial shockable rhythm[†]	665 (42%)	648 (41%)	681 (37%)	663 (36%)	708 (37%)	705 (38%)	640 (36%)	718 (36%)	754 (36%)	807 (37%)	<0.01	295 (2%)
AED defibrillation[†]	140 (9%)	159 (10%)	177 (9%)	206 (11%)	278 (15%)	336 (18%)	353 (20%)	358 (18%)	383 (18%)	456 (21%)	<0.01	82 (0.4%)

Abbreviations: AED, automated external defibrillator; CPR, cardio-pulmonary resuscitation; NR not reported *Data represents 4 months **Data represents 6 months ***Median (25^{th} to 75^{th} percentile), trend in time tested using Jonckheere-Terpstra test. [†]Variables are denoted as cases (percentage), trend in time tested using Chi-square statistic. [‡]Oslo, North Holland and Stockholm regions: time EMS call to scene arrival. Copenhagen region: time of dispatch of the first ambulance to scene arrival

Table 2. Baseline and resuscitation characteristics of OHCA patients with presumed cardiac cause and residential location

Baseline characteristics	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	*P* for trend	Missing n (%)
Patients, n	1100	1126	1319	1323	1362	1301	1257	1389	1487	1517		
Copenhagen, n	NR	NR	272	320	286	218	182	173	192	157		
Oslo, n	96	90	34*	NR	NR	NR	NR	94**	212	173		
Stockholm, n	409	420	429	396	445	438	455	503	484	500		
North Holland, n	595	616	584	607	631	645	620	619	599	687		
Age***	71 (59, 80)	70 (59, 80)	71 (60, 80)	71 (61, 81)	72 (62, 81)	71 (60, 81)	72 (62, 81)	71 (62, 81)	71 (61, 81)	72 (62, 81)	<0.01	61 (<1%)
Male sex†	747 (68%)	729 (65%)	843 (64%)	844 (64%)	866 (64%)	819 (63%)	785 (63%)	905 (65%)	966 (65%)	985 (65%)	0.56	17 (<1%)
Bystander CPR†**	551 (50%)	646 (58%)	621 (49%)	648 (50%)	695 (52%)	731 (57%)	758 (61%)	951 (69%)	987 (67%)	1041 (69%)	<0.01	170 (1%)
Witnessed collapse†	769 (70%)	770 (69%)	857 (67%)	817 (63%)	855 (64%)	771 (61%)	760 (61%)	856 (63%)	870 (59%)	888 (59%)	<0.01	188 (1%)
Time call to scene arrival***‡	9 (7,12)	10 (8,13)	9 (6,12)	8 (6,12)	9 (6,12)	8 (6,11)	8 (6,11)	9 (7,12)	9 (6,12)	8 (6,11)	<0.01	1548 (12%)
Initial shockable rhythm†	370 (34%)	372 (33%)	357 (27%)	358 (28%)	382 (28%)	383 (30%)	333 (27%)	367 (27%)	407 (28%)	405 (27%)	<0.01	211 (2%)
AED defibrillation†	74 (7%)	80 (7%)	74 (6%)	86 (7%)	132 (10%)	153 (12%)	161 (13%)	161 (12%)	177 (12%)	214 (14%)	<0.01	61 (0.5%)

Abbreviations: AED, automated external defibrillator; CPR, cardio-pulmonary resuscitation; NR not reported *Data represents 4 months **Data represents 6 months ***Median (25th to 75th percentile), trend in time tested using Jonckheere-Terpstra test. †Variables are denoted as cases (percentage), trend in time tested using Chi-square statistic. ‡Oslo, North Holland and Stockholm regions: time EMS call to scene arrival. Copenhagen region: time of dispatch of the first ambulance to scene arrival

Proportion of shockable initial rhythm in relation to defibrillator connection time

Figure 3 shows the proportion of SIR in relation to defibrillator connection time. If time from EMS-call to defibrillator connection was 8-10 minutes, the proportion of SIR was still 48% (95%CI 46-51). For this delay, the proportion of SIR for OHCA at a residential location was 41% (95%CI 38-43) and for OHCA in a public location 71% (95%CI 67-75). Results divided in Period 1 and Period 2 are shown in eFigure 1.

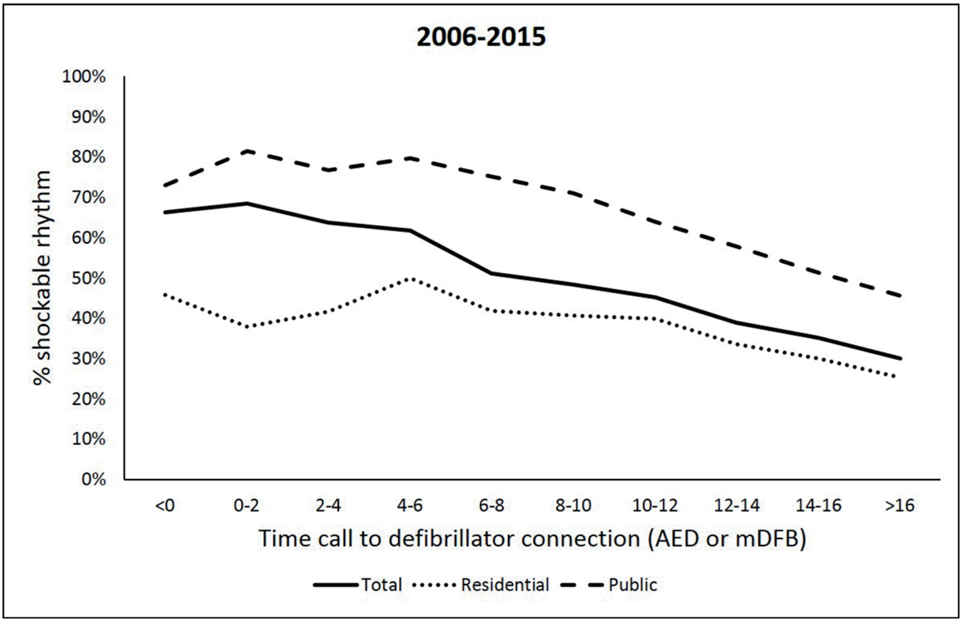

Figure 3. Proportion shockable initial rhythm and time to defibrillator connection in minutes (2006-2015)

Abbreviations: AED, automated external defibrillator; mDFB, manual defibrillator

Table 3. Baseline and resuscitation characteristics of OHCA patients with presumed cardiac cause and public location

Baseline characteristics	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	*P* for trend	Missing n (%)
Patients, n	508	498	595	560	555	550	553	652	664	699		
Copenhagen, n	NR	NR	80	94	76	97	74	98	94	95		
Oslo, n	61	39	22*	NR	NR	NR	NR**	50	72	88		
Stockholm, n	191	198	204	204	227	201	230	221	221	232		
North Holland, n	256	261	289	262	252	252	249	283	277	284		
Age***	65 (56, 75)	65 (56, 76)	64 (54, 75)	64 (55, 76)	65 (54, 74)	64 (55, 75)	66 (55, 75)	66 (55, 75)	65 (55, 76)	66 (55, 75)	0.55	137 (2%)
Male sex†	425 (84%)	398 (80%)	491 (83%)	461 (82%)	444 (80%)	454 (83%)	445 (81%)	527 (82%)	534 (81%)	568 (82%)	0.57	24 (<1%)
Bystander CPR†**	346 (69%)	348 (70%)	437 (75%)	407 (73%)	414 (76%)	446 (82%)	436 (81%)	533 (82%)	530 (81%)	593 (86%)	<0.01	64 (1%)
Witnessed collapse†	411 (81%)	401 (81%)	461 (79%)	424 (76%)	416 (77%)	418 (78%)	416 (78%)	476 (75%)	487 (75%)	531 (77%)	0.01	93 (2%)
Time call to scene arrival***‡	9 (6,12)	9 (7,13)	8 (5,11)	8 (5,11)	8 (6,12)	8 (5,11)	9 (6,12)	9 (6,12)	9 (6,11)	8 (6,11)	0.04	637 (11%)
Initial shockable rhythm†	294 (59%)	274 (57%)	324 (56%)	305 (55%)	325 (60%)	321 (59%)	307 (56%)	350 (55%)	346 (53%)	399 (58%)	0.24	101 (2%)
AED defibrillation†	65 (13%)	79 (16%)	103 (18%)	120 (22%)	146 (26%)	182 (33%)	192 (35%)	197 (30%)	206 (31%)	242 (35%)	<0.01	20 (0.5%)

Abbreviations: AED, automated external defibrillator; CPR, cardio-pulmonary resuscitation; NR not reported *Data represents 4 months **Data represents 6 months ***Median (25^{th} to 75^{th} percentile), trend in time tested using Jonckheere-Terpstra test. †Variables are denoted as cases (percentage), trend in time tested using Chi-square statistic. ‡Copenhagen data includes: time of dispatch of the first ambulance to vehicle stop

Discussion

Main findings

Over the total study period (2006-2015), the proportion of SIR declined in four regions from four European countries and this decline was primarily observed in OHCAs at residential locations. However, when limiting the analysis to more recent study years (2011-2015), the proportion of SIR remained stable. When time from EMS-call to defibrillator connection time was short (8-10 minutes), the proportion of SIR was still high with 41% for OHCA at a residential location, and 71% for OHCA in a public location.

Levelling off of decline in SIR and prior literature

Although a decline in proportion of SIR was present in Period 1, we found that the decline in SIR has levelled off during Period 2. The decline in SIR in Period 1 may result from an absolute decrease of patients at risk for SIR or from an absolute increase in non-SIR OHCAs. First, an absolute decrease of patients at risk for a SIR may be a result of primary prevention measures and/or medical changes that resulted in improved treatment of ischemic heart disease (e.g., more use of β-adrenoceptor blockers) and/or more widespread use of implantable cardioverter defibrillators.[4,13] Second, an absolute increase in non-SIR OHCAs may result from population changes such as higher aged OHCA patients. Also, it has been suggested that co-morbidities such as obstructive pulmonary disease has been associated with non-SIR OHCAs, whereby recent studies suggested an increasing disease burden in OHCA patients (in particular with advancing age).[14,15]

The levelling off in the decline of the proportion of SIR observed in Period 2 may, at least partly, be influenced by an increasing rate of bystander CPR and the stabilized rate of witnessed status (while this rate decreased in Period 1). Being witnessed during collapse and an increased chance on receiving bystander CPR reduces the no-flow time, which may lead to slower degeneration of a SIR.[16] Nonetheless, these variables did not statistically explain the absence of decline in SIR during Period 2.

AED initiatives and presence of SIR

Controlled clinical trials have shown that the use of AEDs in public settings by trained citizen-responders improves survival after OHCA.[17] OHCA patients at a residential location differ unfavourably from OHCA patients in a public location.[7,18] In combination with a (presumed ongoing) decline in proportion of a SIR[4], this gave rise to the question whether AED initiatives are worthwhile for OHCA patients at residential locations.

Results from the present study showed that the observed decline in SIR has levelled off, in particular in OHCAs occurring at a residential location. In addition, the present study adds important information, as we can demonstrate that the proportion of SIR in OHCA patients at a residential location with a short delay (8-10 minutes) between EMS-call and defibrillator connection is still high. This cut-off point of 8-10 minutes is important

because many international EMS systems adopted a 8-minute response time for EMS units responding to life-threatening events (i.e., in order to maximize survival chances after OHCA).[19]
Furthermore, rates of AED defibrillation doubled during the study period. As previously shown, use of AEDs at a residential location decreases time from EMS-call to defibrillator connection and is associated with increased survival rates in patients with a SIR[20]. We therefore recommend continuous efforts to improve resuscitation care at residential locations, with strong emphasis on introducing or extending AED initiatives to facilitate early defibrillation (such as public access defibrillation programs).[21] This recommendation is important, in particular, because approximately 70% of OHCAs occur at a residential location while survival rates after OHCA occurring at home are significantly lower than after OHCA occurring in public places.[8] Thus, for residential locations, even a modest increase in survival would have a substantial impact in absolute numbers of lives saved.

Differences in proportion of SIR across study sites

Differences in proportions of SIR have been observed across the study sites. This may be a result of regional differences in inclusion in the registry, since the definition of an EMS-treated OHCA differs across the sites. For instance, in the Netherlands, an OHCA is included in the registry if the OHCA is treated by the EMS for >2 minutes. The definition in Oslo includes a duration of >30 seconds EMS treatment and in Denmark no minimal duration is used. Therefore, the included proportion of OHCAs with a worse prognosis may have been higher in the Scandinavian regions when compared to the Dutch region, resulting in a lower proportion of SIR. Also, OHCA patients with AED defibrillation only and ROSC at arrival of the ambulance were not included in the Oslo registry, whereas these cases (with high chances of presenting with a SIR) were included in the other registries. However, the use of AEDs was very low in the Oslo registry.

Limitations

Some important limitations need to be considered; first, as with all observational studies, we were only able to study associations. A causal relation between any of the variables studied cannot be determined in this cohort. Second, missing data occurred as not every site collected data of each study year (i.e., missing data for the years 2006-2007 [Copenhagen] and 2009-2012 [Oslo]. Finally, although all study regions used the Utstein template to collect data, differences may exist because of: (1) variation in the interpretation of the Utstein definitions; (2) regional differences in the EMS system and (3) differences in inclusion to the registries, as mentioned above. To attenuate the effect of these differences between participating study regions, we chose to use proportions instead of incidences. Also, we stratified results by study region and performed a multilevel analysis.

Strengths

A major strength of the present study is the comprehensiveness of the collected data sets, including data from EMS-dispatch centre, paramedics and hospital thereby providing a complete picture of the circumstances of the OHCAs.

Conclusion

A small decline in proportion of SIR was observed in the study period 2006-2015, in particular in OHCAs occurring at a residential location. In the second half of this study period (2011-2015), this decline has levelled off.

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Competing interests

None declared.

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2

Supplementary materials

eTable 1. Baseline and resuscitation characteristics of OHCA patients with presumed cardiac cause by location

Baseline characteristics	Residential	Public	*P* value	Missing n (%)
Patients, n (%)	13181 (69%)	5834 (31%)		39 (<1%)
Copenhagen, n (%)	1800 (72%)	708 (28%)		
Oslo, n (%)	699 (68%)	332 (32%)		
Stockholm, n (%)	4479 (68%)	2129 (32%)		
North Holland, n (%)	6203 (70%)	2665 (30%)		
Age*	71 (61, 81)	65 (55, 75)	<0.01	201 (1%)
Male sex†	8489 (65%)	4747 (82%)	<0.01	80 (<1%)
Bystander CPR†**	7629 (59%)	4490 (78%)	<0.01	273 (1%)
Witnessed collapse†	8213 (63%)	4441 (77%)	<0.01	320 (2%)
Time call to scene arrival*‡	9 (6,12)	8 (6,12)	<0.01	2188 (11%)
Initial shockable rhythm†	3734 (29%)	3245 (57%)	< 0.01	3 51 (2%)

Abbreviations: CPR, cardio-pulmonary resuscitation *Median (25th to 75th percentile) †Variables are denoted as cases (percentage) ‡Oslo, North Holland and Stockholm regions: time EMS call to scene arrival. Copenhagen region: time of dispatch of the first ambulance to scene arrival

eTable 2. Baseline and resuscitation characteristics of OHCA patients with presumed cardiac cause, Copenhagen

Baseline characteristics	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	***P* for trend**	**Missing n (%)**
Copenhagen, n	NR	NR	352	414	362	315	256	271	286	252		
Age*	NR	NR	69 (58, 80)	70 (59, 82)	70 (56, 81)	67 (56, 78)	71 (61, 82)	70 (60, 82)	70 (60, 80)	70 (59, 79)	0.43	37 (1%)
Male sex†	NR	NR	228 (65%)	251 (61%)	228 (63%)	197 (64%)	150 (59%)	177 (67%)	171 (61%)	162 (66%)	0.61	29 (1%)
Public location†	NR	NR	80 (23%)	94 (23%)	76 (21%)	97 (31%)	74 (29%)	98 (36%)	94 (33%)	95 (38%)	<0.001	-
Bystander CPR†	NR	NR	99 (31%)	141 (35%)	139 (39%)	156 (50%)	132 (53%)	163 (62%)	161 (59%)	177 (72%)	<0.001	90 (4%)
Witnessed collapse†	NR	NR	198 (61%)	248 (62%)	220 (61%)	180 (58%)	142 (57%)	155 (59%)	156 (56%)	130 (53%)	0.01	76 (3%)
Time dispatch to scene arrival*‡	NR	NR	5 (4,7)	5 (4,7)	6 (4,8)	5 (4,7)	5 (4,6)	5 (4,7)	5 (4,8)	5 (4,7)	0.26	33 (1%)
Initial shockable rhythm†	NR	NR	76 (22%)	100 (24%)	89 (25%)	82 (26%)	65 (25%)	74 (27%)	72 (22%)	59 (23%)	0.36	-
AED defibrillation†	NR	NR	12 (4%)	20 (5%)	13 (4%)	10 (3%)	14 (6%)	15 (6%)	17 (6%)	17 (7%)	0.32	61 (2%)

Abbreviations: AED, automated external defibrillator; CPR, cardio-pulmonary resuscitation; NR not reported *Median (25^{th} to 75^{th} percentile), trend in time tested using Jonckheere-Terpstra test. †Variables are denoted as cases (percentage), trend in time tested using Chi-square statistic.

eTable 3. Baseline and resuscitation characteristics of OHCA patients with presumed cardiac cause, Oslo

Baseline characteristics	2006	2007	2008*	2009	2010	2011	2012	2013**	2014	2015	*P* for trend	Missing n (%)
Oslo, n	158	130	56	NR	NR	NR	NR	144	287	263		
Age***	71 (57, 80)	69 (60, 78)	72 (62, 81)	NR	NR	NR	NR	71 (62, 80)	69 (56, 80)	71 (62, 82)	0.19	-
Male sex†	118 (75%)	81 (52%)	47 (84%)	NR	NR	NR	NR	107 (74%)	215 (76%)	194 (74%)	0.27	4 (0.4%)
Public location†	61 (39%)	39 (30%)	22 (39%)	NR	NR	NR	NR	50 (35%)	72 (25%)	88 (34%)	0.10	7 (<1%)
Bystander CPR†**	87 (56%)	85 (66%)	21 (41%)	NR	NR	NR	NR	114 (79%)	231 (81%)	215 (82%)	<0.001	9 (<1%)
Witnessed collapse†	111 (71%)	91 (71%)	37 (66%)	NR	NR	NR	NR	97 (67%)	193 (68%)	198 (75%)	0.63	8 (<1%)
Time call to scene arrival***‡	10 (8,13)	10 (8,14)	10 (9,13)	NR	NR	NR	NR	9 (6,11)	8 (7,11)	8 (6,11)	<0.001	6 (<1%)
Initial shockable rhythm†	73 (47%)	49 (38%)	19 (34%)	NR	NR	NR	NR	53 (36%)	104 (37%)	104 (40%)	0.25	5 (<1%)
AED defibrillation†	17 (8%)	13 (7%)	4 (6%)	NR	NR	NR	NR	8 (4%)	12 (3%)	14 (3%)	0.001	25 (2%)

Abbreviations: AED, automated external defibrillator; CPR, cardio-pulmonary resuscitation; NR not reported *Data represents 4 months **Data represents 6 months ***Median (25^{th} to 75^{th} percentile), trend in time tested using Jonckheere-Terpstra test. †Variables are denoted as cases (percentage), trend in time tested using Chi-square statistic.

eTable 4. Baseline and resuscitation characteristics of OHCA patients with presumed cardiac cause, Stockholm

Baseline characteristics	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	***P* for trend**	**Missing n (%)**
Stockholm, n	602	624	635	601	672	640	685	725	706	746		
Age*	71 (61, 82)	72 (60, 82)	71 (60, 81)	71 (61, 82)	71 (62, 81)	71 (60, 83)	71 (61, 82)	71 (62, 82)	72 (62, 82)	72 (63, 82)	0.02	128 (2%)
Male sex†	418 (69%)	410 (66%)	430 (68%)	412 (69%)	463 (69%)	441 (69%)	451 (66%)	497 (69%)	486 (69%)	499 (67%)	0.86	5 (<1%)
Public location†	191 (32%)	198 (32%)	204 (32%)	204 (34%)	227 (34%)	201 (32%)	230 (34%)	221 (31%)	221 (31%)	232 (32%)	0.55	28 (<1%)
Bystander CPR†	253 (42%)	299 (48%)	334 (53%)	293 (49%)	338 (50%)	350 (55%)	366 (53%)	461 (64%)	397 (56%)	450 (60%)	<0.001	9 (0.1%)
Witnessed collapse†	408 (68%)	410 (66%)	411 (65%)	360 (60%)	408 (62%)	380 (63%)	418 (63%)	419 (59%)	418 (60%)	441 (59%)	<0.001	111 (2%)
Time call to scene arrival*‡	10 (7,16)	10 (7,15)	10 (7,14)	10 (7,15)	11 (8,15)	10 (7,15)	10 (7,16)	11 (8,18)	11 (8,15)	10 (7,14)	0.28	36 (<1%)
Initial shockable rhythm†	161 (27%)	177 (29%)	166 (27%)	164 (28%)	218 (33%)	192 (30%)	180 (27%)	174 (24%)	180 (26%)	204 (28%)	0.28	68 (1%)
AED defibrillation†	31 (5%)	36 (6%)	40 (6%)	28 (5%)	60 (9%)	75 (12%)	65 (10%)	66 (9%)	59 (8%)	89 (12%)	<0.001	3 (<1%)

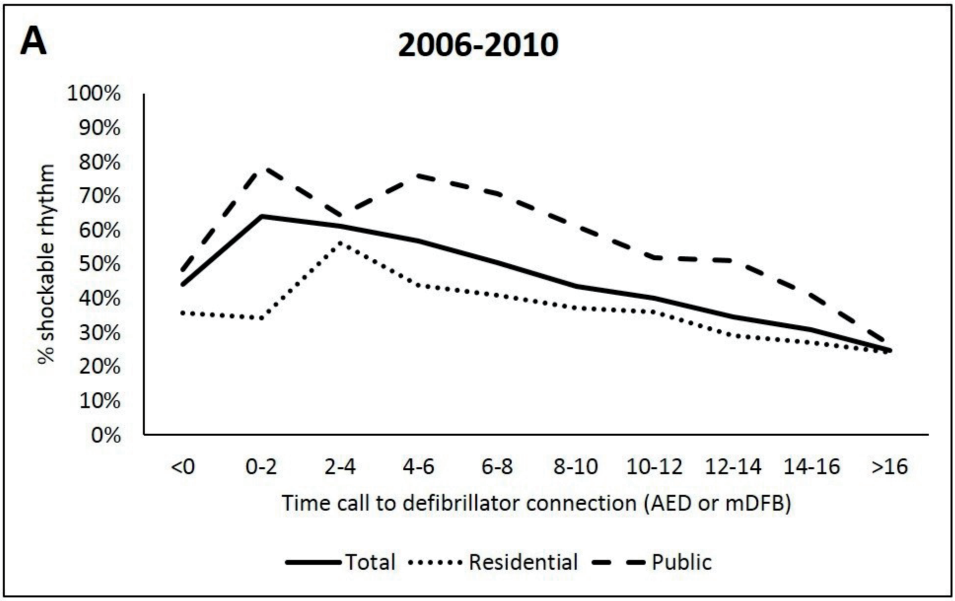
Abbreviations: AED, automated external defibrillator; CPR, cardio-pulmonary resuscitation; NR not reported *Median (25^{th} to 75^{th} percentile), trend in time tested using Jonckheere-Terpstra test. †Variables are denoted as cases (percentage), trend in time tested using Chi-square statistic.

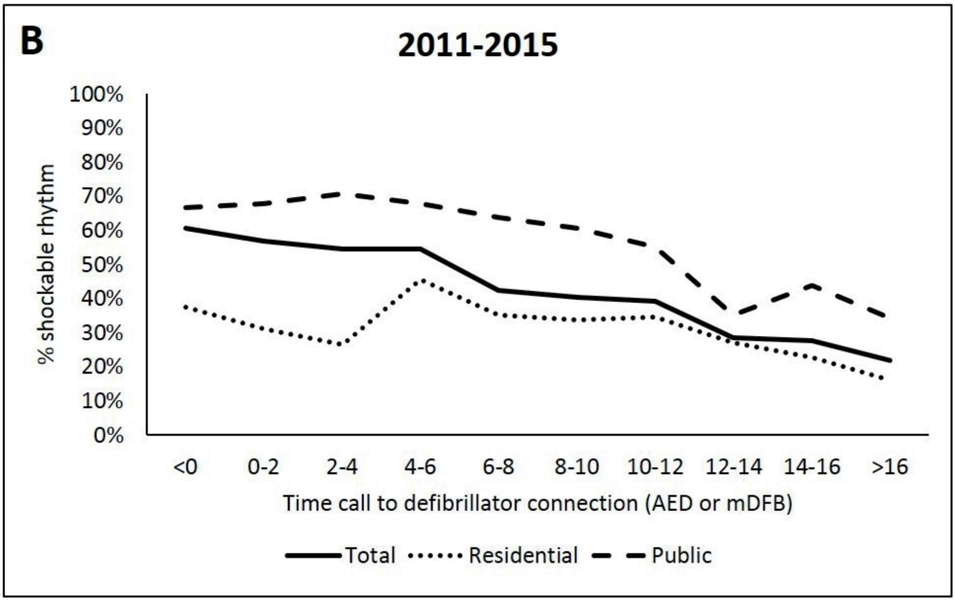
eTable 5. Baseline and resuscitation characteristics of OHCA patients with presumed cardiac cause, North-Holland

Baseline characteristics	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	***P* for trend**	**Missing n (%)**
North Holland, n	851	877	873	869	886	897	870	902	876	971		
Age*	67 (56, 76)	67 (56, 77)	66 (56, 77)	67 (57, 78)	69 (59, 79)	68 (57, 78)	68 (58, 78)	67 (58, 78)	68 (57, 78)	68 (58, 77)	<0.01	36 (<1%)
Male sex†	639 (75%)	640 (73%)	631 (73%)	642 (74%)	621 (70%)	636 (71%)	629 (72%)	651 (72%)	630 (72%)	707 (73%)	0.24	4 (<1%)
Public location†	256 (30%)	261 (30%)	289 (33%)	262 (30%)	252 (29%)	252 (28%)	249 (29%)	283 (31%)	277 (32%)	284 (29%)	0.76	4 (<1%)
Bystander CPR†	557 (66%)	615 (71%)	606 (71%)	622 (73%)	635 (74%)	671 (76%)	696 (81%)	746 (83%)	731 (84%)	803 (84%)	<0.001	127 (1%)
Witnessed collapse†	662 (78%)	674 (77%)	674 (78%)	634 (74%)	646 (75%)	629 (71%)	616 (71%)	662 (74%)	593 (68%)	657 (69%)	<0.001	89 (1%)
Time call to scene arrival‡	9 (7,11)	9 (7,11)	9 (7,11)	10 (7,12)	9 (7,11)	8 (6,10)	8 (6,11)	8 (6,11)	9 (7,11)	8 (7,11)	<0.001	2108 (24%)
Initial shockable rhythm†	431 (52%)	422 (49%)	420 (49%)	399 (47%)	401 (46%)	431 (49%)	395 (46%)	417 (48%)	398 (47%)	440 (47%)	0.030	240 (3%)
Time to first monitored rhythm*	10 (8,12)	11 (8,13)	10 (7,13)	10 (7,13)	9 (7,11)	8 (5,11)	8 (6,10)	8 (7,11)	8 (6,10)	8 (6,10)	<0.001	646 (7%)
AED connection†	183 (22%)	211 (24%)	208 (24%)	293 (34%)	385 (44%)	460 (51%)	515 (51%)	538 (60%)	569 (65%)	642 (66%)	<0.001	2 (<1%)
AED defibrillation†	94 (11%)	114 (13%)	121 (14%)	158 (18%)	205 (23%)	251 (28%)	274 (32%)	270 (30%)	295 (34%)	337 (35%)	<0.001	2 (<1%)

Abbreviations: AED, automated external defibrillator; CPR, cardio-pulmonary resuscitation; NR not reported *Median (25th to 75th percentile), trend in time tested using Jonckheere-Terpstra test. †Variables are denoted as cases (percentage), trend in time tested using Chi-square statistic.

eFigure 1, Proportion of shockable initial rhythm and time from EMS call to defibrillator connection





A: Proportion shockable initial rhythm and time to defibrillator connection in minutes (2006-2010);
B: Proportion shockable initial rhythm and time to defibrillator connection in minutes (2011-2015);
Abbreviations: AED, automated external defibrillator; mDFB, manual defibrillator

2

PART 2

The use of automated external defibrillators and new technologies

CHAPTER 3

European First Responder systems and differences in return of spontaneous circulation and survival after out-of-hospital cardiac arrest: a study of registry cohorts

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Background

In Europe, survival rates after out-of-hospital cardiac arrest (OHCA) vary widely between regions. Whether a system dispatching First Responders (FRs; main FR-types: firefighters, police officers, citizen-responders) is present or not may be associated with survival rates. This study aimed to assess the association between having a dispatched FR-system and rates of return of spontaneous circulation (ROSC) and survival across Europe.

Methods

Results of an inventory of dispatched FR-systems for OHCA in Europe were combined with aggregate ROSC and survival data from the EuReCa-TWO study and additionally collected data. Regression analysis (weighted on number of patients included per region) was performed to study the association between having a dispatched FR-system and ROSC and survival rates to hospital discharge in the total population and in patients with shockable initial rhythm, witnessed OHCA and bystander cardiopulmonary resuscitation (CPR; Utstein comparator group). For regions without a dispatched FR-system, the theoretical survival rate if a dispatched FR-system would have existed was estimated.

Findings

We included 27 European regions. There were 15,859 OHCAs in the total group and 2,326 OHCAs in the Utstein comparator group. Aggregate ROSC and survival rates were significantly higher in regions with an FR-system compared to regions without (ROSC: 36% [95%CI 35%-37%] vs. 24% [95%CI 23%-25%]; $P<0.001$; survival in total population [N=15.859]: 13% [95%CI 12%-15%] vs. 5% [95%CI 4%-6%]; $P<0.001$; survival in Utstein comparator group [N=2326]: 33% [95%CI 30%-36%] vs. 18% [95%CI 16%-20%]; $P<0.001$), and in regions with more than one FR-type compared to regions with only one FR-type. All main FR-types were associated with higher survival rates (all $P<0.050$).

Interpretation

European regions with dispatched FRs showed higher ROSC and survival rates than regions without.

Introduction

When treating out-of-hospital cardiac arrest (OHCA), a swift pre-hospital response is essential. If the delay in response is too long, an initial shockable rhythm may dissolve into a non-shockable rhythm, thereby decreasing survival chances.[1] The use of automated external defibrillators (AEDs) before Emergency Medical Service (EMS) arrival reduces the time from call to defibrillation of OHCA-patients with a shockable initial rhythm, thereby increasing their chances on survival.[2] To increase the likelihood of immediate provision of cardiopulmonary resuscitation (CPR) and rapid defibrillation with an AED, systems that dispatch First Responders (FRs) have been developed all over Europe.[3,4] Because the implementation of such systems may be influenced by local circumstances and policies, there is a wide variety of dispatched FR-systems, both between and within European countries.[5] At present, over 50% of European countries have a dispatched FR-system to respond to a suspected OHCA in place.[5]

Survival rates after OHCA vary widely between European regions.[6] Whether a dispatched FR-system is present or not may contribute to this variation. The number and type(s) of dispatched FR may also play a role (FR-system may dispatch one or more of the following types of FR: [1] firefighters, [2] police officers, [3] citizen-responders). For instance, it was estimated that, in a region in the Netherlands where firefighters and police officers are dispatched as FRs, 7% of OHCA-patients would not have received a first shock within six minutes if citizen-responders would not also have been dispatched.[7] On the other hand, an additional gain in OHCA survival rate upon dispatch of a second or third FR-type may level-off as the number of dispatched FR-types increases, because of the competing contribution of each FR-type.[8]

This study aimed to assess if having a dispatched FR-system is associated with higher rates of return of spontaneous circulation (ROSC) and survival to hospital discharge across Europe. Second, we aimed to assess if European regions with more than one dispatched FR-type have higher rates of ROSC and survival than European regions with one dispatched FR-type. Finally, for European regions without a dispatched FR-system, we aimed to estimate the theoretical survival rate that would be achieved if a dispatched FR-system would have existed.

Methods

Design and data collection

This research was conducted as part of the ESCAPE-NET project that aims to discover the causes of and best treatments for OHCA.[9] Results of a previous study (FR-ONE), which

inventoried all current dispatched FR-systems for OHCA across 29 European regions (countries [if one FR-system applied to the total country] or parts thereof [if individual regions within one country used a specific FR-system])[5], were combined with published aggregate ROSC and survival results from the EuReCa-TWO study[6] and additionally collected survival rates. EuReCa-TWO was a prospective study, for which data were collected from 28 European regions in the period October 1, 2017 - December 31, 2017. Because FR-ONE was not performed during the same study period as EuReCa-TWO, the information on FR-systems that was collected during the FR-ONE study was updated by re-consulting the OHCA professionals that contributed to FR-ONE.[5]
OHCA-patients per study region and their corresponding aggregate rates of survival to hospital discharge came from two sources: 1) the EuReCa-TWO published survival rates, and 2) by contacting the coordinator of the OHCA registry when different FR-systems existed within one EuReCa region or when survival data were not published in the EuReCa-TWO study. This applied to the following regions: Province of Pavia (Italy), Region of Emilia Romagna (Italy), Region of Stockholm (Sweden), Region of Marburg-Biedenkopf (Germany), and the Region of Hradec Kralove (Czech Republic). To obtain survival rates from these regions, the coordinators of the OHCA-registry were contacted through the ESCAPE-NET FR-ONE and EuReCa network. All data collected complied with the Utstein definitions.[10]

Definitions

A dispatched FR-system was defined as a system in which a dispatch centre directs persons not on medical duty to attend OHCA events and initiate early CPR and possibly early defibrillation. FR-types studied in the present study were: dispatched firefighters, police officers, and citizen-responders. An extensive description of FRs and EMS per region is provided in Supplementary materials: definitions.
Regions were categorized into one of three categories of comparable size: (1) region without FRs; (2) region with one FR-type, and (3) region with >one FR-type. ROSC was defined as a period of at least 30 seconds of pre-hospital ROSC. The Utstein comparator group was defined as the group of patients with a shockable initial rhythm (defined as pulseless ventricular-tachycardia or ventricular-fibrillation) and a bystander witnessed-OHCA.[11]

Outcomes

The primary outcome was defined as pre-hospital ROSC-rate and survival to hospital discharge rate in the total study population ($\text{survival}_{\textbf{total}}$), and the secondary outcome was survival rate to hospital discharge of the Utstein comparator group ($\text{survival}_{\textbf{comparator}}$).

Data analysis as performed per protocol

Rates of ROSC and survival were reported as mean (95% Confidence Interval [CI]). Weighted regression analysis (based on number of patients included per region) was used to study the association between having a dispatched FR-system and rates of (1) ROSC, (2) $survival_{total}$, and (3) $survival_{comparator}$.

First, the association between FR-type and OHCA survival was evaluated using weighted regression analysis. For the categorical variable: "FR-type", two dummy variables were created. Next, main FR-types were analysed as a binary variable (FR-type dispatched [either alone or complementary to other FR-types in one FR-system] vs. FR-type not dispatched) using weighted regression analysis. As a post-hoc exploratory analysis, we performed a weighted regression analysis to explore a possible association between having a dispatched FR-system and rates of bystander-CPR.

Finally, for regions without a dispatched FR-system and without missing data (Spain, Croatia, Hungary, Italy [Province of Pavia], France and Serbia), we estimated the theoretical change between observed and expected $survival_{total}$ rate to estimate the Survival rate in these regions if a dispatched FR-system would have existed. The observed rate was the mean survival rate as reported in the EuReCa-TWO study and/or additionally collected data through the ESCAPE-NET FR-ONE study network. The expected rate was calculated by multiplying the observed rate of a region without an FR-system by the relative increase in mean survival rate between regions with and without an FR-system. The relative increase was calculated as (mean rate in regions with dispatched FR-system - mean rate in regions without dispatched FR-system)/mean rate in regions without dispatched FR-system. This is described in more detail in Supplementary materials methods: theoretical increase. To calculate these estimations, we assumed that the following changes take place after implementation of an FR-system: (1) the proportion of OHCA-patients in the Utstein comparator group would increase, because the proportion of patients with a shockable initial rhythm would increase (due to a shorter response time) and (2) survival increase would be more substantial for patients in the Utstein comparator group than for patients outside of it (non-comparator group) as patients with a non-shockable initial rhythm and unwitnessed OHCA are less likely to benefit from early defibrillation and CPR.

Statistical tests were two-tailed, with $P<0.05$ considered statistically significant, and performed in SPSS (version 24.0 for Mac). To account for multiple comparisons, the significance level was set at $P\leq0.01$ for the linear regression analyses.

Results

First Responder systems in Europe

In total, 27 European regions were included (Table 1). Of 22 from the 29 FR-ONE regions, data could be combined with the aggregate data of EuReCa-TWO; of 5 from the 29 FR-ONE regions additional aggregate data was collected by contacting the coordinator of the OHCA registry and of 2 from the 29 FR-ONE regions data could not be retrieved (Supplementary materials: data collection per region).

The updated results from the FR-systems inventory showed that more than half (17 of 27) of the regions had an FR-system in place (Figure 1), including 10 regions with one FR-type and 7 regions with >one FR-type (Table 1). Geographical clustering of dispatched FR-types in Europe was not observed.

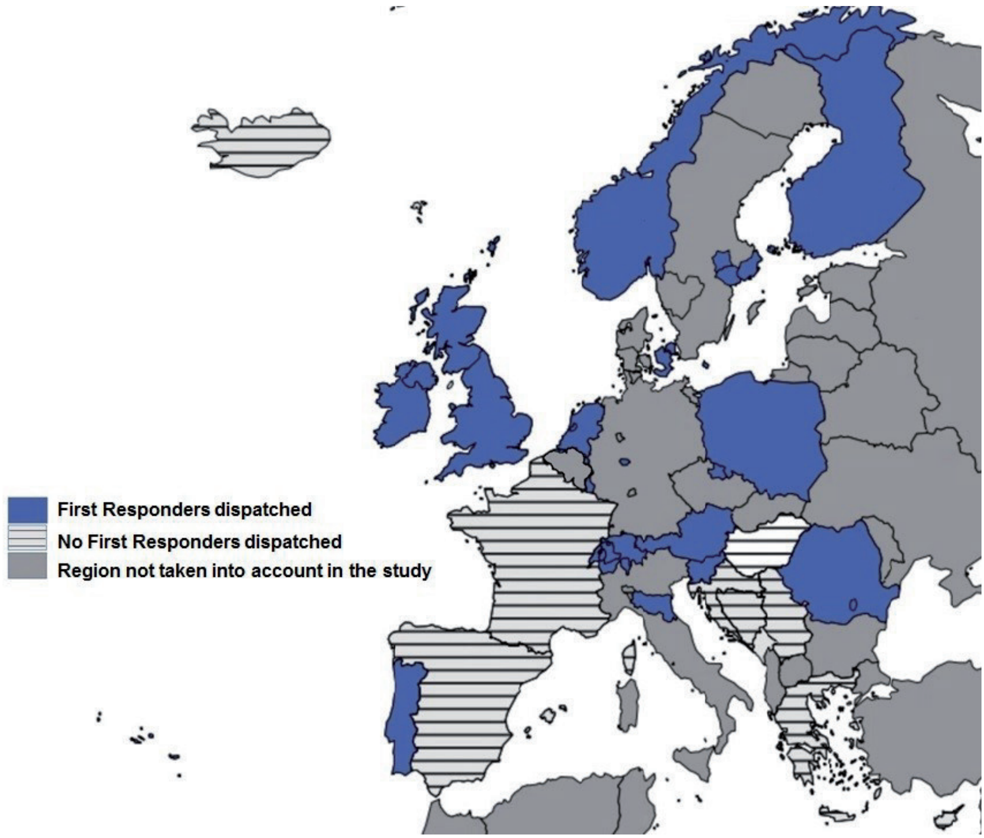

Figure 1 Overview of First Responders in Europe
Figure shows European regions that do dispatch First Responders in the event of an out-of-hospital cardiac arrest and regions that do not.

Table 1. Overview per study region

Country (N=Population served)	First Responder types (N)	OHCA confirmed (N)	Total population of cardiac OHCAs included for analyses – CPR started (N)	CPR started (%)	ROSC rate of total population	Survival rate of total population	Utstein comparator group (N)	Survival rate of Utstein comparator group
First Responders dispatched		**N=10,038**	**N=7,948**				**N=1,116**	
Austria N=3.444.711	Police officers (1)	457	348	76%	35%	8%	73	19%
Czech Republic (Hradrec Kralove) N=92.921	Firefighters, citizen-responders, police officers (3)	91	83	91%	55%	13%	18	39%
Germany (Marburg-Biedenkopf) N=245.013	Citizen-responders (1)	38	38	(100%)	45%	18%	7	43%
Denmark (Copenhagen) N=1.821.577	Citizen-responders (1)	391	331	85%	42%	12%	56	55%
Finland N=4.138.648	Firefighters (1)	1133	565	51%	41%	15%	113	41%
Ireland N=4.757.97	Firefighters, citizen-responders, police officers, off duty EMS (4)	870	592	68%	25%	7%	83	32%
Italy (Emilia Romagna) N=4.449.000	Firefighters, citizen-responders, police officers, taxi drivers (4)	52	52	(100%)	52%	27%	17	59%
Luxembourg N=549.680	Firefighters (1)	138	64	46%	29%	Missing	12	Missing
The Netherlands N=3.869.347	Firefighters, police officers, citizen-responders (3)	574	440	77%	43%	19%	123	45%
Norway N=5.267.128	Firefighters (3)	711	711	(100%)	28%	12%	121	39%
Poland N=3.385.000	Firefighters (1)	739	382	52%	32%	8%	57	25%
Portugal N=514.531	Firefighters (1)	99	52	53%	35%	Missing	Missing	Missing
Romania N=4.086.753	Firefighters, citizen-responders (2)	642	463	72%	16%	Missing	42	0%
Sweden (Stockholm) N=1.553.000	Firefighters, citizen responder, police officers (3)	202	202	(100%)	Missing	10%	29	28%
Switzerland N=2.415.000	**	432	264	61%	31%	Missing	47	10%
Slovenia N=1.209.479	Firefighters (1)	284	176	68%	38%	13%	41	32%
United Kingdom N=20.245.023	**	3185	3185	(100%)	41%	9%	277	27%

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Country (N=Population served)	First Responder types (N)	OHCA confirmed (N)	Total population of cardiac OHCAs included for analyses – CPR started (N)	CPR started (%)	ROSC rate of total population	Survival rate of total population	Utstein comparator group (N)	Survival rate of Utstein comparator group
First Responders not dispatched		**N=13,393**	**N=7,911**				**N=1,210**	
Bosnia & Herzegovina N=110.979	None	46	22	79%	Missing	0%	Missing	Missing
Cyprus N=650.000	None	103	46	28%	20%	0%	Missing	Missing
France* N=9.993.658	None	2433	2276	94%	19%	5%	341	20%
Greece N=8.146.660	None	1129	742	36%	7%	Missing	52	11%
Hungary N=9.797.561	None	3430	1993	58%	23%	4%	299	12%
Croatia N=1.895.000	None	429	284	66%	22%	9%	54	24%
Iceland N=237.538	None	40	Missing	75%	43%	Missing	Missing	Missing
Italy (Pavia) N=547.251	None	204	204	(100%)	24%	6%	15	20%
Serbia N=1.227.069	None	405	197	49%	20%	7%	41	10%
Spain N=31.751.584	None	5174	2147	41%	37%	11%	408	32%

Abbreviations: EMS, emergency medical system; NA, Not Applicable; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation
*Firefighters are considered EMS
**Region was only taken into account in the main analysis (First Responders available versus First Responder not available). Region was left out in the sub-analyses with number and type of First Responders, as this could not be determined accurately.

ROSC and survival rates of regions with First Responder system vs. no First Responder system

The number of OHCAs included for ROSC and survival analyses was 15,859 in the total group (N=7,948 in regions with an FR-system, N=7,911 in regions without an FR-system) and 2,326 in the Utstein comparator group (N=1,210 in regions with an FR-system, N=1,116 in regions without an FR-system). Rates of ROSC and survival per study region are shown in Table 1.

Mean ROSC-rates were significantly higher in regions with an FR-system than in regions without an FR-system (36% [95%CI 35%-37%] vs. 24% [95%CI 23%-25%], *P*=0.001). Also, mean survival rates were significantly higher in regions with an FR-system than in regions without an FR-system in both the total population and the Utstein comparator group (mean $survival_{total}$ 13% [95%CI 12%-14%] vs. 5% [95%CI 4%-6%], *P*=0.001; mean $survival_{comparator}$ 33% [95%CI 30%-36%] vs. 18% [95%CI 16%-20%], *P*=0.001).

The post-hoc exploratory analysis showed that regions with an FR-system showed higher bystander-CPR rates than regions without an FR-system (mean 59% [95%CI 58%-60%] vs. 46% [95%CI 45%-47%] P=0.003).

Association between number and type of FR-systems, and survival rates

Regions dispatching one FR-type and regions dispatching one FR-type had significantly higher mean ROSC-rates than regions that do not dispatch FRs: 34% [95%CI 32%-36%] vs. 24% [95%CI 23%-25%] *P*=0.001 and 40% [95%CI 39%-41%] vs. 24% [95%CI 23%-25%] *P*=0.001, respectively (Figure 2A). Moreover, regions dispatching >one FR-type had significantly higher mean ROSC-rates than regions dispatching only one FR-type: mean 40% [95%CI 39%-41%] vs. 34% [95%CI 32%-46%], *P*=0.001 (Figure 2A).

Similar results were observed when survival rates were studied. For $survival_{total}$ this was as follows**:** (1) one FR-type vs. no FR-type: mean 12% [95%CI 11%-13%] vs. 5% [95%CI 4%-6%]; *P*=0.006; (2) >one FR-type vs. no FR-type: mean 14% [95%CI 13%-15%] vs. 5% [95%CI 4%-6%]; *P*<0.005 and (3) >one FR-type vs. one FR-type: mean 14% [95%CI 13%-15%] vs. 12% [95%CI 4%-6%]; *P*=0.015 (Figure 2A). For $survival_{comparator}$: (1) one FR-type vs. no FR-type: mean 32% [95%CI 28%-35%] vs. 18% [95%CI 16%-20%]; *P*=0.003; (2) >one FR-type vs. no FR-type: mean 39% [95%CI 36%-43%] vs. 18% [95%CI 16%-20%]; *P*=0.002 and (3) >one FR-type vs. one FR-type: mean 39% [95%CI 36%-43%] vs. 32% [95%CI 28%-35%]; *P*=0.022 (Figure 2B).

Presence of any of the FR-types was statistically significantly associated with higher survival rates (Supplementary materials: results).

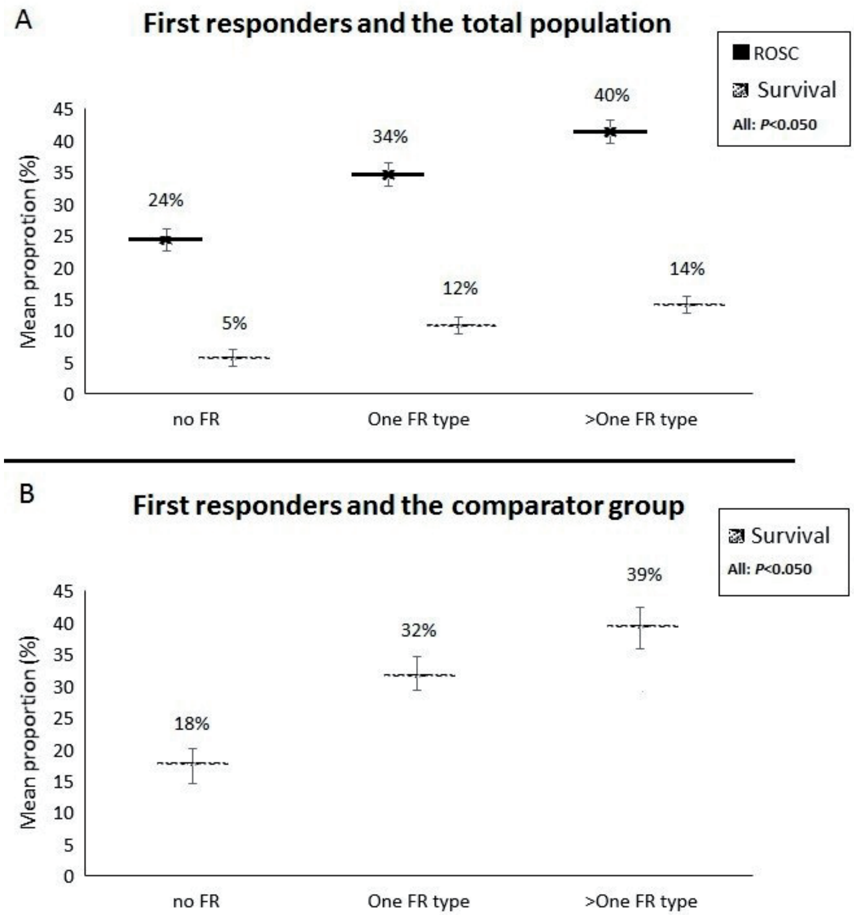

Figure 2 First Responder system and survival rates

Figure shows **(A)** ROSC and the survival rate in the total population and **(B)** the survival rate in the Utstein comparator group; per dispatched First Responder category (No First Responders, One First Responder type, >One First responder type). P values indicate the differences between FR categories (groups compared: 1. One First responder type vs. No First Responders, 2. >One First responder type vs. No First Responder type and 3. >One First responder type vs. One First Responder type). The line within a First Responder category corresponds to the 95% Confidence Interval

Calculated theoretical survival rates

The mean proportion of OHCA-patients in the Utstein comparator group was 1.36 times higher in regions with an FR-system than in regions without (19% vs. 14%, respectively, Table 2). The mean survival rate in the Utstein comparator group was 1.83 times higher in regions with an FR-system than in regions without (33% vs. 18%). The mean survival rate in the non-comparator group was 1.67 times higher in regions with an FR-system than in regions without (5% vs. 3%). With these calculated relative increases, we estimated survival**total** rates for Spain, Croatia, Hungary and Italy (Province of Pavia), if an FR-system would have existed (Table 2): Spain, from observed 11% to estimated 23%; Croatia, from 9% to 17%; Hungary, from 4% to 7%; Italy (Province of Pavia), from 6% to 8%; France, from 5% to 10% and Serbia from 7% to 8% (Table 2). Also, the following survival**comparator** rates were estimated: Spain, from observed 32% to estimated 59%; Croatia, from 24% to 44%; Hungary, from 12% to 22%; Italy (Province of Pavia), from 20% to 37%; France from 20% to 37% and Serbia from 10% to 18%.

Table 2. Estimations of survival rates in regions without First Responder systems if a First Responder system would have been in place

Calculations used to determine the theoretical survival rate (from observed to expected)		**No FR-system** *Mean %*	**FR-system dispatched** *Mean %*	**Relative increase*:** *FRs system dispatched vs. no FR-system*
1.	Proportion of OHCA-patients in Utstein comparator group	14% (95%CI 13%-15%)	19% (95%CI 18%-20%)	36% (*1.36)
2.	Survival rate in Utstein comparator group	18% (95%CI 17%-19%)	33% (95%CI 32%-34%)	83% (*1.83)
3.	Survival rate in non-Utstein comparator group	3% (95%CI 3%-3%)	5% (95%CI 5%-5%)	67% (*1.67)

		OHCA-patients		**OHCA survivors**		
Country	**Total group N**	**Comparator group %****	**Non-comparator group %****	**Survivaltotal %****	**Comparator group %****	**Non-comparator group %****
Observed rates						
Spain	2147	19% (95%CI 17%-21%)	81% (95%CI 79%-83%)	11% (95%CI 10%-12%)	32% (95%CI 27%-37%)	6% (95%CI 5%-7%)
Croatia	284	19% (95%CI 14%-24%)	81% (95%CI 76%-86%)	9% (95%CI 6%-12%)	24% (95%CI 13%-35%)	4% (95%CI 1%-7%)
Hungary	1993	15% (95%CI 13%-17%)	85% (95%CI 83%-87%)	4% (95%CI 3%-5%)	12% (95%CI 8%-16%)	2% (95%CI 0%-4%)
Italy (Pavia)	204	7% (95%CI 3%-11%)	93% (95%CI 89%-97%)	6% (95%CI 3%-9%)	20% (95%CI 0%-41%)	3% (95%CI 0%-5%)
France÷	2276	15% (95%CI 14%-16%)	85% (95%CI 84%-86%)	5% (95%CI 4%-6%)	20% (95%CI 16%-24%)	2% (95%CI 1%-3%)
Serbia	197	14% (95%CI 9%-19%)	86% (95%CI 81%-91%)	7% (95%CI 3%-11%)	10% (95%CI 0%-21%)	3% (95%CI 0%-6%)

	Total group N	Comparator group N (%)	Non-comparator group N (%)	Survivaltotal N (%)	Comparator group N (%)	Non-comparator group N (%)
Expected rates						
Spain	2147	558 (26%; 95%CI 24%-28%)***	1589**** (74%; 95%CI 72%-76%)	488 (23%; 95%CI 21%-25%)±	329 (59%; 95%CI 55%-63%)‡	159†† (10%; 95%CI 9%-11%)‡‡
Croatia	284	74 (26%; 95%CI 21%-31%)***	210**** (74% 95%CI 69%-79%)	48 (17%; 95%CI 13%-21%)±	33 (44%; 95%CI 33%-55%)‡	15†† (7%; 95%CI 4%-10%)‡‡
Hungary	1993	399 (20%; 95%CI 18%-22%)***	1594**** (80%; 95%CI 78%-82%)	136 (7%; 95%CI 6%-8%)±	88 (22%; 95%CI 18%-26%)‡	48†† (3%; 95%CI 2%-4%)‡‡
Italy (Pavia)	204	20 (10%; 95%CI 6%-14%)***	184**** (90%; 95%CI 86%-94%)	16 (8%; 95%CI 4%-12%)±	7 (37%; 95%CI 16%-58%)‡	9†† (5%; 95%CI 2%-8%)‡‡
France÷	2276	455 (20%; 95%CI 18%-22%)	1821**** (80%; 95%CI 78%-82%)	223 (10%; 95%CI 9%-11%)±	168 (37%; 95%CI 33%-41%)‡	55 (3%; 95%CI 2%-4%)‡‡
Serbia	197	37 (19%; 95%CI 14%-24%)	160*** *(81%; 95%CI 69%-86%)	15 (8%; 95%CI 12%-12%)±	7 (18%; 95%CI 6%-30%)‡	8 (5%; 95%CI 2%-8%)‡‡

Abbreviations: FR, first responder; OHCA, out-of-hospital cardiac arrest

*Relative increase was calculated as (mean (FR-system dispatched) – mean (No FR-system)) / (mean (No FR-system))

**N is not reported for observed rates, only percentages could be collected accurately based on published data

***Proportion in comparator group (expected): proportion comparator group (observed) *1.36 [=relative increase proportion patients in comparator group]

****Non-comparator, N (expected) = N total – N comparator (expected)

‡Proportion survival in comparator group (expected): proportion survival in comparator group (observed) * 1.83 [=relative increase survival comparator group]

‡‡Proportion survival in non-comparator group (expected): proportion survival in non-comparator group (observed) * 1.67 [=relative increase survival non-comparator group]

±Proportion $survival_{total}$ (expected): N patients survived comparator (expected) + N patients survived non-comparator (expected) / N Total

÷Firefighters are part of the EMS in France. Therefore, the calculated expected survival rate only applies to the situation in which either citizen-responders or police officers will be added to an EMS system with firefighters being part of the EMS

Discussion

Main findings

In the present study, we included 27 different European regions. More than half (17 of 27) of the regions had an FR-system in place.

European regions dispatching FRs (either one FR-type or more than one FR-type dispatched) have significantly greater rates of ROSC and survival after OHCA when compared to regions that do not have a dispatched FR-system. This is in line with prior research regarding FR-systems for ROSC[12] and for OHCA survival.[13] Moreover, modestly greater ROSC and OHCA survival rates were observed in regions dispatching more than one FR-type when compared to regions dispatching one single FR-type.

Presence of any of the main dispatched FR-types (firefighters, police officers and citizen-responders) was statistically significant associated with greater survival rates.

Number of FR-types per system dispatched

Our study showed that the differences in number of FR-types dispatched (within one FR-system) may contribute to differences in ROSC and OHCA survival rates across Europe. When dispatching more than one FR-type, a modest but significant increase in both ROSC and OHCA survival rate was observed when compared to dispatching one single FR-type. A second or third dispatched FR-type may provide an early defibrillation shock to OHCA-patients who may not have received an early shock if the FR-system was limited to one or two FR-type(s) as observed in a prior study from the Netherlands.[7] This could possibly increase ROSC and OHCA survival rate. However, the increase in ROSC and OHCA survival rate was only modest when more than one FR-type was dispatched compared to one single FR-type and (for survival) not statistically significant after we reduced the *P* value to ≤0.01. A study from 2005 showed that equipping police cars with AEDs in an urban area in the United States where firefighters are dispatched did not improve OHCA Survival rate to hospital discharge.[8] It is possible that the increase in OHCA survival rate may level-off with an increasing number of dispatched FR-types, because of their competing contribution to the OHCA chain of care. In our study, there were too few observations to analyse the association of FR-systems dispatching two or three different FR-types with survival, thus not allowing for comparisons between two or three dispatched FR-types.

It was already observed in 1996 that an increase in OHCA survival may be associated with the use of a two-tier EMS system (the additional dispatch of BLS-providers or firefighters) as opposed to a one-tier EMS system[14] and that changing from a one-tier to a two-tier EMS system might be an attractive cost-effective option.[15] However, recent studies into the relation between dispatching FR-types and its health-economic impact that could provide insight into the costs and benefits are scarce. A previous study from the Netherlands that *dispatched* AED use during resuscitation showed no association with lower in-hospital health care costs (nor with higher costs).[16] Another study from Ireland showed that an increased number of AEDs alone is unlikely to improve survival in a cost-effective manner, though the study does suggest that strategic deployment of AEDs by CPR-trained FRs may be an important link in OHCA survival.[17] Future research in the health economic field is needed.

Type of dispatched FR

The FR-ONE study showed that firefighters feature highly as FR-types in Europe[5]. Other prior research suggested that firefighters have a role in increasing OHCA survival rate.[13,18-20] Also, FR-systems involving police officers and/or dispatched citizen-responders may be promising.[13,21,22] In line with prior research, the present study observed that all main FR-types individually may contribute to higher OHCA survival rates. Based on these results and supported by results from a prior study[5], we could hypothesize that it is less important which specific FR-type is dispatched but that differences between characteristics of the main FR-types, such as whether the FR-type is trained in CPR or not, may play a larger role.[5] For instance, although frequent CPR-training is a feature of most dispatched FR-systems in Europe, some regions allow citizen-responders to register without validation of CPR-training.[5] Also, differences in response capabilities between FR-types and/or the method of alerting FR-types may influence OHCA survival rates.[5] For example, if an FR-type is based at the EMS station (which is the case in some European regions) it may not be worthwhile to dispatch that particular FR-type. Being stationed at the same location as the EMS thus may result in that FR-type being rarely dispatched.

First Responder systems and OHCA survival rate

We found that survival rates after dispatching FRs were higher both in the total population and in the Utstein comparator group. Previous findings from Sweden indicated that the main impact of FR treatment on OHCA survival was seen in patients with a shockable initial rhythm.[13]

We studied survival rates at hospital discharge and were not able to study survival rates at hospital admission. Differences in Survival rate at hospital discharge may be partly due to differences in in-hospital treatment. Yet, a previous Swedish study showed that a higher proportion of patients was admitted to the hospital alive when FRs were dispatched, indicating that higher OHCA survival rates are likely achieved, at least in part, through prehospital actions by FRs.[13]

To reduce possible effects of differences in in-hospital treatment on differences in survival to discharge in our present analysis, we also investigated ROSC. In line with the observed higher survival rates, regions dispatching FRs also showed higher ROSC-rates. However, the difference in ROSC-rate between regions where FRs are dispatched and regions where FRs are not dispatched was much smaller when compared to the difference in survival rate at hospital discharge (a relative increase in ROSC-rate of 50% was observed in regions dispatching FRs, while a relative increase in survival rate of 160% was observed). This may, for example, suggest that regions with a dispatched FR-system in place could transfer OHCA-patients to hospitals that provide better post resuscitation care than those in locations without FRs. Another possibility is that in regions with an FR-system the time interval between the start of OHCA to ROSC is shorter or that OHCA-patients receive higher CPR-quality from FRs. Patients who achieve ROSC earlier will arrive in a better condition and thus may have a higher chance of survival once admitted to the hospital.[25] However, we have no data available to explore the possibilities as mentioned above.

Implementation of a First responder system and raising awareness of CPR

Our calculations regarding the theoretical change in survival for regions without an FR-system may suggest that, if an FR-system would be implemented, this might result in a higher OHCA survival rate in all regions, assuming that having an FR-system is associated with survival.

Public health programs for raising awareness of CPR in the community have been implemented in many countries.[26,27] Among others, the following public programs were associated with increased bystander-CPR provision: mandatory CPR-education in elementary schools and voluntary CPR-training in the community.[27]

It could also be that introducing an FR-system is a proxy for increased public awareness of the need of bystander-CPR in case of OHCA. Higher awareness (after implementation of an FR-system) might be associated with a higher likelihood of bystander-CPR and subsequently, favourable survival outcomes after OHCA.[26] Our post-hoc analysis suggesting a higher rate of bystander-CPR in regions with an FR- system may support this line of thinking.

Implementation of an FR-system may be part of a combined approach of several initiatives to improve the OHCA-chain of care. [28] Therefore, the benefit of the presence of an FR-system may also be a result of other beneficial improvements in the chain of care (for example, having an organization goal).[29]

Strengths and limitations

This study has several strengths. First, data harmonization within the ESCAPE-NET project and EuReCa-TWO study made it possible to analyse the association between FR-systems and OHCA survival rates.[9] Second, all analyses were weighted based on the number of included patients per region in order to take account of the variation by chance in regional estimates.

Nonetheless, multiple limitations need to be considered. First, we used aggregate data only, since patient-level data were not available. This limited our possibilities to address confounding. Furthermore, our aggregate data originated from different registries. Hence, differences in inclusion criteria may exist, which may hamper the comparability of ROSC and survival rates (i.e. differences in % CPR initiated across the registries).We addressed this issue by using the Utstein comparator group. Second, the effectiveness of FRs depends among others on the response time of the EMS. In a system with short EMS response times, dispatched FRs may have less added value than in a system with longer EMS response times. Also, the effectiveness of a system might be better assessed by AED-connection rate. However, EMS response intervals and AED-connection rates were not available in each of the participating regions. Nonetheless, our analysis of the Utstein comparator group only includes OHCA-patients with an initial shockable rhythm. A shockable initial rhythm eliminates most cases (>50%) with more than 10-12 minutes delay from call EMS to connection to AED or manual defibrillator, thus rendering more comparable groups.[30] Third, other unmeasured differences between the included regions may have affected the results of this study, such as differences in population characteristics or in-hospital treatment. The association found in this study should prompt further research to determine the size of the effect of FR-systems when other differences between regions are adjusted for. Also, we have no information on the proportion of FRs being first on scene and the actual percentage of AED-connection rate by FRs. Finally, as with all observational studies, we were only able to study associations. A causal relation between FR-systems and survival could therefore not be determined; inference and quantification of the effect of implementing an FR-system must be done with caution.

Conclusion

European regions dispatching First Responders after OHCA (either dispatching one single FR-type or more than one FR-type) have significantly higher rates of ROSC and survival to hospital discharge than regions that do not dispatch FRs. Having a dispatched FR-system, dispatching at least one FR-type (firefighters, police officers, citizen-responders) for OHCA might increase survival rate in Europe, but further prospective or randomized research is required.

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Supplementary materials

Supplementary methods: definitions

Definition EMS and First Responders (extended)

Emergency Medical Service (EMS)
An EMS is defined as a service dedicated to providing out-of-hospital acute medical care. EMS includes ambulance or responding vehicle, and/or helicopter services dispatched by a dispatch centre to provide acute medical care and to transport the patient to a hospital equipped to provide acute care.
All European regions included for the present study dispatch an ambulance in the event of an OHCA. The ambulance is part of the EMS and may be supported by a helicopter. The ambulance is nurse lead (non-physicians) in most European countries. In several countries (e.g. Germany, Spain and Denmark) a physician or firefighters (France) may also be part of the standard EMS.

First-Responder (FR)
In 2000, the American Heart Association and the International Liaison Committee on Resuscitation defined three levels of responders.[22] Level one is 'Traditional Responders' and includes those whose role it is to respond in an emergency, e.g., police officers and fire fighters. Level two are 'Citizen-responders', and level three are responders to those at high risk (e.g., family members of high-risk patients). For this study, the definition of FRs includes level one and two responders, but is limited to individuals who are dispatched to the event. In summary, for the purposes of this study, FRs are defined as all individuals who are *not* on-duty members of the EMS and are *dispatched* by a dispatch centre to attend OHCA events.

Dispatched FR treatment included:

- Members of the general population who respond independently or as part of a community-based citizen-responder group which is linked to the ambulance service
- Firefighters or police officers;

Dispatched FR treatment does not include:

- On-duty ambulance staff, regardless of whether they were alerted to the scene or arrived on scene by chance (e.g., when they came across an OHCA event *en route* to another call);
- Any individual who arrived on scene by chance, regardless of his/her level of expertise.

FRs that are not dispatched by a dispatch centre were not considered in this study. In every region included in the present study, FRs either carry an AED (firefighters and police officers) or are directed by the dispatch centre to the OHCA victim or to the nearest publicly accessible AED to bring it to the OHCA victim (citizen responders).

Supplementary methods: Theoretical increase in survival rate

A relative increase was calculated as follows: mean [FR system dispatched] – mean [No FR system]] / mean [No FR system].

To estimate the theoretical increase in survival rate, we calculated the following:
(1) the expected proportion of OHCA patients included within the Utstein comparator group, calculated by multiplying the observed proportion of OHCA patients within the Utstein comparator group, with the **relative** increase in mean proportion of patients included in the Utstein comparator group between regions without a dispatched FR system and regions with a FR system; (2) the expected survival rate within the Utstein comparator group, calculated by multiplying the observed survival**comparator** rate with the **relative** increase in mean survival**comparator** rate between regions without a dispatched FR system and regions with a FR system, and (3) the expected survival rate for patients outside the comparator group (the non-comparator group), calculated by multiplying the observed survival**non-omparator** rate with the **relative** increase in mean survival**non-omparator** rate for patients outside the comparator group between regions without a dispatched FR system and regions with a FR system. Since we used percentages of aggregate data to calculate the estimations, we applied rounded percentages in each calculation.

Supplementary results: data collected per region

Included regions and data originated from

Country (region, if specified)		ROSC and survival data originated from
1.	Austria (Upper Austria, Lower Austria, Salzburg, Tyrol, Styria and Vorarlberg)	EuReCa TWO
2.	Bosnia-Herzegovina	EuReCa TWO
3.	Croatia	EuReCa TWO
4.	Cyprus	EuReCa TWO
5.	Denmark (Copenhagen)	EuReCa TWO
6.	Finland	EuReCa TWO
7.	France	EuReCa TWO
8.	Greece	EuReCa TWO
9.	Hungary	EuReCa TWO
10.	Iceland (Region of Akureyri)	EuReCa TWO
11.	Ireland	EuReCa TWO
12.	Luxembourg	EuReCa TWO
13.	The Netherlands (North-Holland province)	EuReCa TWO
14.	Norway	EuReCa TWO
15.	Poland	EuReCa TWO
16.	Portugal	EuReCa TWO
17.	Romania	EuReCa TWO
18.	Serbia	EuReCa TWO
19.	Slovenia	EuReCa TWO
20.	Spain	EuReCa TWO
21.	Switzerland	EuReCa TWO
22.	United Kingdom	EuReCa TWO
23.	Italy (Province of Pavia)	Contacting the coordinator of the OHCA registry
24.	Italy (Region of Emilia Romagna)	Contacting the coordinator of the OHCA registry
25.	Sweden (Region of Stockholm)	Contacting the coordinator of the OHCA registry
26.	Germany (Region of Marburg-Biedenkopf)	Contacting the coordinator of the OHCA registry
27.	Czech Republic (Hradec Kralove)	Contacting the coordinator of the OHCA registry
28.	Estonia	Data could not be collected
29.	Malta	Data could not be collected

Supplementary results: FR type and survival rates

Main FR type	**Part of the system***	**Not part of the system****	***P* value**
	Survival**comparator,** (95%CI)	Survival**comparator,** Mean (95%CI)	
Firefighters	33 (30-36)	22 (19-25)	<0.01
Police officers	33 (29-37)	26 (24-28)	<0.01
Citizen responders	32 (29-35)	26 (23-29)	0.02
	Survival**total,** Mean (95%CI)	Survival**total,** Mean (95%CI)	
Firefighters	13 (12-14)	7 (6-8)	<0.01
Police officers	13 (12-14)	9 (9-10)	<0.01
Citizen responders	13 (12-14)	8 (7-9)	<0.01

Abbreviations: FR, First Responder; CI Confidence Interval
*Dispatched as an FR in the FRs system (either dispatched alone of dispatched complementary to other main FR types)
**Not dispatched as a FR (either no FR system or not dispatched as a FR type in an existing FR system

CHAPTER 4

4

Transfer of essential AED information to treating hospital (TREAT)

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Background

Defibrillation in out-of-hospital cardiac arrest (OHCA) is increasingly performed by using an Automated External Defibrillator (AED). Therefore presence of a shockable rhythm is recurrently only documented by the AED. However, AED-information is rarely available to the treating physician.

Purpose

To determine 1) how often a shockable rhythm was recorded only in the AED; 2) if so, how often information that a shockable rhythm had been present reached the physician.

Methods

Data on OHCA patients with (presumed) cardiac cause with an AED connected in the years 2012-2014 (Study period 1) and 2016 (Study period 2) in the Amsterdam Resuscitation Study (ARREST) database were collected. We determined how often only the AED had defibrillated. In these patients, we retrospectively analyzed EMS run sheets and hospital discharge letters to determine if a shockable rhythm and/or AED use was correctly noted. In Study period 2, we prospectively contacted the physicians to study whether AED defibrillation was known.

Results

In Study period 1, of 2840 OHCA CPR attempts with (presumed) cardiac cause, 1521 (54%) patients had a shockable rhythm, with 356 patients (13%) receiving AED defibrillation only. Of these patients, 11 hospital discharge letters (4%) contained no information about a shockable rhythm. In Study period 2, 125/1128 patients (11%) received AED defibrillation only; of these, in two cases the shockable rhythm was unknown by the physician.

Conclusion

In 11-13% of OHCAs, a shockable rhythm is only seen on the AED-ECG. Adequate transfer to the physician of vital AED-information is essential but not always accomplished

Introduction

Defibrillation in out-of-hospital cardiac arrest (OHCA) is increasingly performed by bystanders and dispatched first responders (police, firefighters or citizen-responders) before arrival of Emergency Medical Services (EMS), using automated external defibrillators (AEDs). [1-4] The use of on-site or dispatched AEDs reduces the time from emergency call to defibrillation and increases survival chances of patients with a shockable initial rhythm (ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT)).[5-7] In the Netherlands in 2012 an AED was connected to the patient before EMS arrival in as much as 60% of all EMS attended resuscitation attempts.[6]

Early defibrillation by an AED may not require further EMS shocks and EMS personnel may not be aware that a shockable rhythm had been present.[8] Most AEDs lack an ECG display, and retrieving ECGs stored in the AED requires dedicated device-specific software and connection tools. Retrieving the AED-ECG registration on the scene is therefore too problematic and time-consuming. The availability of information on the initial rhythm (or delivery of an AED shock) to the treating physician depends on an oral account of the person who employed the AED to EMS personnel and subsequently to the physician in the treating hospital. The hectic emergency setting at an OHCA scene and in the emergency department hampers accurate information transfer of this vital information.[9] Also, AED users may not transfer information on the presence of a shockable rhythm to EMS personnel because they may be unaware of its importance for diagnosis and clinical decision-making during post-resuscitation care.[10] Conversely, an incorrect shock advice by the AED, for instance due to chest compressions during rhythm analysis, may result in an incorrect diagnosis as well.[11] Thus, increased AED use may paradoxically have led to a lack of correct information on presence of a shockable rhythm, due to an inadequate transfer of this key information to the treating physician.

A shockable initial rhythm is a strong predictor for favourable outcome and guides the physician to the cause of the OHCA.[6,12,13] For instance, detailed ECG information such as type of shockable rhythm and response to delivered shock, is instrumental when implantation of an implantable cardioverter defibrillator (ICD) is considered.[14] The aim of this study is to determine 1) how often a shockable heart rhythm was stored only in an AED; 2) in such situations, how often information that a shockable rhythm had been present reached the treating physician at the hospital.

Methods

Study design and patient population

We analyzed data from the ARREST registry. This ongoing registry prospectively collects data of all EMS-attended out-of-hospital cardiac arrests in the province North Holland, a contiguous region (population 2,4 million with rural and urban areas) in the Netherlands since July 2005. The registry was established to identify determinants of risk and outcome of OHCA.[6,15] The present study includes the years 2012 -2014 (Study period 1) and the year 2016 (Study period 2). In both periods all OHCA with a (presumed) cardiac cause, a shockable rhythm (recorded by the AED or EMS manual defibrillator) and an AED connected before EMS arrival were included. We excluded patients who died within 24 hours after admission (since for these patients providing AED ECG information would not serve a treating purpose) and patients with non-shockable rhythm during the entire AED connection. The medical ethics review board of the Amsterdam UMC, Academic Medical Center (AMC), approved the study including the use of data of deceased patients. Deferred informed consent (because of the medical emergency setting) was obtained from all surviving patients.

First responder and EMS system in the study region

In a medical emergency, people dial the national emergency number. When the emergency medical service dispatcher suspects an OHCA, two ambulances are dispatched, often together with a first responder (fire fighters and police) equipped with an AED ("dispatched AED") and qualified to perform basic life support. Also, citizen-responders are activated by a text message from the dispatch center to either go directly to the victim or retrieve a local AED first. Ambulance personnel are equipped with a manual defibrillator (never with an AED) and are qualified to perform advanced life support. The placement of AEDs in public areas ("onsite AED") was stimulated by (local) government and the Dutch Heart Foundation but not centrally controlled or directed.[5]

Data collection and definitions

After each CPR attempt, EMS paramedics routinely send the continuous ECG from their manual defibrillators to the ARREST study center. All ECGs are stored and analyzed with dedicated software. If a dispatched or onsite AED is used, ARREST personnel visits the AED site shortly after the OHCA and collects the AED ECG recording using AED-specific software. Data items concerning the CPR procedure (e.g., witness of OHCA, bystander CPR performed, and AED use) are collected according to Utstein recommendations by means of a pre-coded set of questions that ambulance staff are required to answer, and by retrieving EMS data of the event.[16] Data on post resuscitation care and survival are derived from hospital records and the civic registry.

A shockable rhythm was defined as ECG documentation (AED or EMS manual defibrillator) of VF or VT. Awareness of shockable rhythm was defined as mentioning of a shock, shockable rhythm or VT/VF in the EMS runsheet and/or discharge letter (Study period 1). Of all patients who were defibrillated using only a dispatched or onsite AED (no defibrillation by EMS), we collected EMS run sheets to establish if the occurrence of an AED shock was indeed transferred from AED users to EMS personnel. We also collected hospital discharge letters to establish how often the occurrence of a shockable rhythm was correctly transferred from EMS personnel to hospital treating physicians. For patients who were only shocked by an AED in Study period 1, we retrospectively analysed ambulance run sheets and hospital discharge letters. For patients who were only shocked by an AED in Study period 2, and were admitted to hospital, we contacted the supervising treating physician by telephone 24-48 hours after OHCA. Data on awareness of the presence of a shockable rhythm and diagnosis were collected according to a predefined set of questions (table 1). Physicians who were not aware that the AED had defibrillated were informed about the AED shock on the shockable rhythm and received the AED ECG for the patient's medical record.

Table 1. Set of questions to treating physician

Questions to treating physician
What is your working diagnosis for the cause of the OHCA in this patient?
Did you know an AED was connected during the resuscitation?
If yes, do you know the AED defibrillated?
In case of the physician did not know about the AED defibrillation:
Did you change your working diagnosis after receiving the information about the AED shock?
What is your final diagnosis about the cause of the OHCA?

Outcome

The primary outcome was the proportion of patients with a shockable rhythm who were only defibrillated by using an AED before EMS arrival. Our secondary outcomes were the proportion of patients where EMS personnel and/or hospital physicians were aware of a shockable rhythm.

Statistical analysis

Categorical variables were presented as percentages and continuous variables as mean ± standard deviation (SD) or as median and interquartile range (IQR) depending on the data distributions.

Results

In Study period 1, 2873 OHCA attempts with a (presumed) cardiac cause were registered (overall 30-day survival 24%; median age 66 years; 72% male); of 33 surviving patients, consent could not be obtained. Of the remaining study population, 1532 patients (54%) had a documented shockable rhythm. Of these, 356 patients (13%) received defibrillation shocks by an AED only (Figure 1a). Of the patients who received AED defibrillation only, 316 patients (89%) were transported to hospital. Of these, 280 patients (79%) were admitted for more than 24 hours and 223 patients (63%) survived to 30 days. In this period, 1308 patients had a non-shockable rhythm and in 674 (52%) of these patients an AED was connected before EMS arrival. In 17 patients (1%) the AED gave an incorrect shock advice due to device related (n=8) and operator-related errors (n=9). Figure 2 shows an example of an operator-related error, due to chest compressions during heart rhythm analysis the AED gives an incorrect shock advise.

In Study period 2, 1128 OHCA attempts with a (presumed) cardiac cause were registered (overall 30-day survival 22%; median age 67 years; 72% male); of 21 surviving patients, consent could not be obtained. Of the remaining study population, 564 patients (51%) had a documented shockable rhythm, defibrillation shocks from an AED only were provided in 125 patients (11%) (Figure 1b). Of the patients who received AED defibrillation only, 102 patients (81%) were transported to the hospital. Of these, 92 patients (74%) were admitted for more than 24 hours and 80 patients (65%) survived to 30 days. In this period , 543 patients had a non-shockable rhythm, 303 (56%) of these patients had an AED connected before EMS arrival. In 7 patients (1%), the AED gave an incorrect shock advice due to device related (n=4) and operator-related errors (n=3).

Baseline characteristics

Table 2 describes the baseline characteristics of patients who received defibrillation shocks from the AED only and were admitted for more than 24 hours. All these patients received bystander CPR before EMS arrival in both study periods. Patients were more often male (79-86%) and the arrest occurred at a public location in the majority of cases (64-66%).

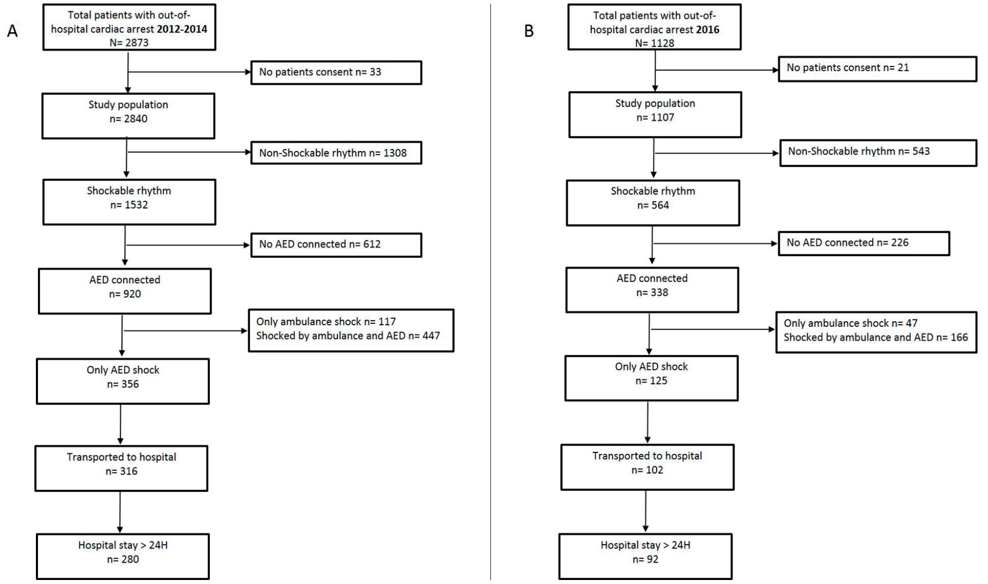

Figure 1.(a) Study period 1 AED connection and defibrillation before EMS arrival. **(b)** Study period 2 AED connection and defibrillation before EMS arrival.

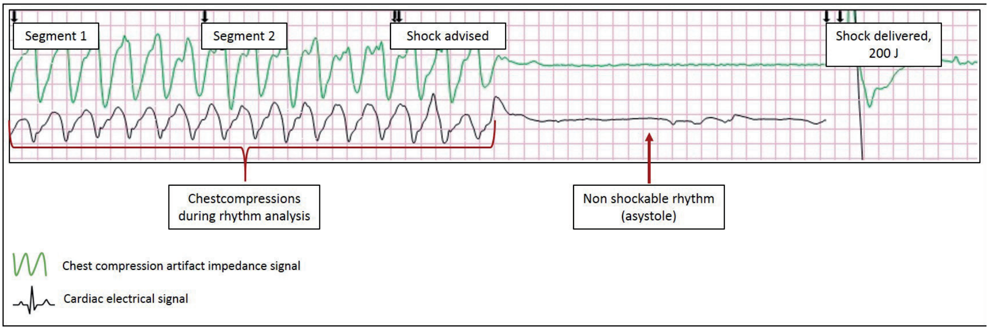

Figure. 2. Operater related error AED, incorrect shock advice due to chest compressions during rhythm analysis. In this example in both AED heart rhythm analysis segments the operater performs chest compression (green chest compression artifact impedance signal). The underlying heart rhythm is asystole (black cardiac electrical signal line) so the operator related error causes an incorrect shock advice and shock delivery.

Table 2. Baseline characteristics OHCA patients with AED connected and shockable rhythm

	2012-2014 N= 280	2016 N=92
Pre-OHCA factors		
Age, years, mean (SD)	63 (15)	65 (12)
Sex, n (%)		
Male	222 (79%)	79 (86%)
Female	58 (21%)	13 (14%)
Location of arrest, n (%)		
Residential	95 (34%)	33 (36%)
Public	185 (66%)	59 (64%)

SD - standard deviation

Proportion of shockable rhythm known by EMS and/or treating physician

In Study period 1, 14 EMS run sheets (6%) did not describe a shockable rhythm or AED defibrillation. Moreover, 11 hospital discharge letters (4%) did not describe a shockable rhythm or AED defibrillation (table 3). The major reported cause of OHCA in the hospital discharge letters of these 11 patients was myocardial infarction. Other reported causes were myocardial ischemia and valve pathology. In Study period 2, 8 (9%) EMS run sheets did not describe a shockable rhythm or AED defibrillation.

Table 3. Shockable rhythm notified to EMS personnel and described in hospital discharge letter

	2012-2014 n=280	2016 n=92
EMS run sheet present	219 (78%)	86 (93%)
Shockable rhythm known	205 (73%)	78 (85%)
Ambulance run sheet missing	61 (22%)	6 (7%)
Hospital discharge letter present	267 (95%)	N/A
Shockable rhythm known	256 (95%)	N/A
Hospital discharge letter missing	13 (5%)	N/A

Knowledge of treating physician about AED connection and presence of shockable rhythm

In Study period 2, we contacted the treating physician of 76 of the 92 patients who were hospitalized for more than 24 hours. In 16 cases the treating physician was not contacted (table 4). In 64 cases (84%), the physician was aware the AED was connected, but in one case, the physician did not know that the AED had defibrillated. In 12 cases (16%) the physician was not aware that an AED had been connected; two times the shockable rhythm was also unknown. In one patient the diagnosis was revised after receiving the information (from collapse with neurologic cause to OHCA with cardiac cause) and after the diagnosis was changed an ICD was subsequently implanted.

Table 4. AED connection and shockable rhythm awareness by treating physician

Call to treating physician	**2016 n= 92**
Treating physician not called n, (%)	16 (17%)
Treating physician approached registry before registry could contact him/her	5
The treating physician was not willing to corporate	3
Reason for not calling is unknown, cases missing	5
Other reasons (patient already discharged or AED ECG impossible to download)	3
Treating physician called n, (%)	76 (83%)
Aware of AED employment	64
Aware of shockable rhythm	63
Not aware of AED employment	12
Aware of shockable rhythm	10

Discussion

Our study showed that in the majority of cases, if during the resuscitation attempt a shockable rhythm was only present during the AED connection, this information was transferred correctly to the EMS personnel and subsequently from the EMS personnel to the treating physician in the admitting hospital. However, in 16% of the cases in our study the physician was not aware of the AED connection before EMS arrival. In two of these cases the physician was also not aware of a shockable rhythm during the resuscitation attempt. In one case the physician did know an AED was connected, but was not aware that the AED had defibrillated. After receiving the AED ECG the original diagnosis was revised and the patient received the correct treatment.

In our study, 26-29% of the analyzed resuscitation attempts an AED defibrillated before arrival of EMS and in 11-13% of the OHCAs only the AED delivered shocks (no further defibrillation by EMS). In comparison with other countries and study regions this is a very high proportion.[1-4] It is important to note that in the ARREST study region, ARREST personnel has been sending AED information to treating physicians if it was noted that a shockable rhythm was only recorded by the AED, for several years before the present study. Hence, treating physicians in the study region are primed to the importance of AED information for patient diagnosis and treatment. This is illustrated by the cases where the treating physician approached the study center in order to obtain the AED ECG information. Therefore, our results are likely overestimating the proportion of adequate transfer to the physician of AED defibrillation.

Initial heart rhythm of an out-of-hospital resuscitation attempt is increasingly registered in AEDs and no longer in EMS manual defibrillators.[8] Treating physicians in regions outside the ARREST study region have no access to ECGs from AEDs, since AED information is not routinely downloaded and made available for patient diagnosis and treatment. The initial heart rhythm is important for diagnosis, clinical decision-making and patient treatment.[10] Information such as type of shockable rhythm (VF or VT; response to delivered shock) is a key element when implantation of an ICD is considered.[14] Also in patients with a non-shockable rhythm, the ECG from the AED can be helpful, e.g., for clinical decision making and correct patient treatment, such as a shock delivered on atrial fibrillation or due to an operator-related error.[11,17]

In other regions, physicians can only use the information on shock delivery reported by the EMS personnel, used as a proxy for the presence of shockable rhythm. Importantly, the correct information about presence of an AED shock is easily lost in the hectic setting or during the multiple information transfers in the chain of care following an out of hospital resuscitation attempt.[9] In addition, many AED users may not be aware that the information the AED has delivered a shock (or not) can be essential information for treatment decisions. It is likely that, if this study had been performed in a region outside the study region, the number of defibrillations by an AED that the physician was unaware of would have been higher than in the present study.

Limitations

First, due to the observational and retrospective design of the study in Study period 1, not all EMS run sheets and hospital discharge letters could be retrieved resulting in missing data on reporting of shockable rhythm and diagnosis. Second, this study was performed in the ARREST study region where physicians are more aware of the importance of AED information, which may have resulted in more correct transfer of AED information and shockable rhythm to treating hospital compared to other regions and countries.

Future research

To estimate the proportion of patients where the information about the AED defibrillation was transferred correctly to EMS and treating physician, research is needed in a setting where treating physicians are not primed to the importance of AED information. Furthermore, we recommend establishing an organized infrastructure to register OHCA and AED deployment, to ensure adequate transfer to the treating physician to make this information readily available for diagnosis and treatment of OHCA patients.

Conclusion

In the Netherlands in a substantial number of OHCAs presence of a shockable rhythm is only registered in the AED memory. Presence of a shockable rhythm on the AED ECG was correctly transferred in the majority of cases. In 6-9% OHCA cases EMS data did not mention a shockable rhythm and in 3-4% information the treating physician was not aware of a shockable rhythm. It is essential for correct patient diagnosis and treatment to retrieve the AED ECG when an AED is used, even if no cardiac cause of the collapse is suspected. Routine retrieval of AED ECGs after AED use in an out-of-hospital resuscitation attempt is required, but is not standard care in the Netherlands, or elsewhere.

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Conflict of interest statement

C.G. received a speaker's fee from Stryker. R.W.K. is the recipient of the unconditional grant of Stryker, Emergency Care, Redmond WA for maintaining the ARREST database.

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CHAPTER 5

5

Analyzing the heart rhythm during chest compressions: performance and clinical value of a new AED algorithm.

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Purpose

Automated external defibrillators (AED) prompt the rescuer to stop chest compressions (CC) for ECG analysis during out-of-hospital cardiac arrest (OHCA). We assessed the diagnostic accuracy and clinical benefit of a new AED algorithm (cprINSIGHT), which analyzes ECG and impedance signals during CC, allowing rhythm analysis with ongoing chest compressions.

Methods

Amsterdam Police and Fire Fighters used a conventional AED in 2016-2017 (control) and an AED with cprINSIGHT in 2018-2019 (intervention). In the intervention AED, cprINSIGHT was activated after the first (conventional) analysis. This algorithm classified the rhythm as "shockable" (S) and "non-shockable" (NS), or "pause needed". Sensitivity for S, specificity for NS with 90% lower confidence limit (LCL), chest compression fractions (CCF) and pre-shock pause were compared between control and intervention cases accounting for multiple observations per patient.

Results

Data from 465 control and 425 intervention cases were analyzed. cprINSIGHT reached a decision during CC in 70% of analyses. Sensitivity of the intervention AED was 96%, (LCL 93%) and specificity was 98% (LCL 97%), both not significantly different from control. Intervention cases had a shorter median pre-shock pause compared to control cases (8 sec vs 22 sec, $p<0.001$) and higher median CCF (86% vs 80%, $P<0.001$).

Conclusion

AEDs with cprINSIGHT analyzed the ECG during chest compressions in 70% of analyses with 96% sensitivity and 98% specificity when it made a S or a NS decision. Compared to conventional AEDs, cprINSIGHT leads to a significantly shorter pre-shock pause and a significant increase in CCF.

Introduction

In out-of-hospital cardiac arrest (OHCA), Automated External Defibrillators (AED) are increasingly used before Emergency Medical Services (EMS) arrive on the scene. The use of on-site or dispatched AEDs reduces the time from call to the first defibrillation and increases survival in patients with a shockable rhythm.[1-5] Traditionally, conventional AED voice prompts instruct the rescuer to interrupt chest compressions for heart rhythm analysis every two minutes.[6, 7] This programmed interruption of chest compressions for rhythm analysis and the delivery of the defibrillation shock may take 12-46 seconds and may account for 20-40% of the time an AED is connected.[8, 9] These interruptions of chest compressions and long pre-shock pauses are an important undesired consequence of the AED algorithm and negatively influence survival: a pre-shock pause of ≥20 seconds was associated with a significant reduction in survival to hospital discharge.[10, 11]

A new algorithm (cprINSIGHT) incorporated in an AED analyzes the heart rhythm during chest compressions, permitting the rescuer to continue cardiopulmonary resuscitation (CPR) during rhythm analysis. When an AED with this new algorithm is used, fewer interruptions of CPR are prompted and decreased hands-off time can be expected. The diagnostic performance and clinical value of such an algorithm incorporated in an AED used in the daily practice of actual cardiac arrest have not been investigated and was identified as an important knowledge gap in the 2015 Consensus on Science on Cardiopulmonary Resuscitation.[12] To assess the clinical value of the algorithm, we analyzed the sensitivity and specificity of its heart rhythm decisions, and compared the chest compression fraction (CCF) and pre-shock pauses with a conventional AED algorithm, during the resuscitation of patients in OHCA.

Methods

Setting, patient population and study design

The study was performed using the infrastructure of the AmsteRdam REsuscitation STudies (ARREST). ARREST is an ongoing prospective registry of all-cause OHCA in North Holland, a province of the Netherlands.[2, 13] The data was collected using the Utstein templates for resuscitation registries.[14] In the study region, when the national emergency number is dialed and the dispatcher suspects an OHCA, two EMS teams are dispatched. In addition, first responders equipped with an AED are dispatched. These first responders are firefighters and police officers trained in Basic Life Support and AED use. Resuscitation was done with a protocol that included a compression: ventilation ratio of 30:2.

We included all patients with an EMS-attended OHCA, for whom an AED was connected by the police and firefighters of Amsterdam. Until 2018, the Amsterdam Police and Amsterdam Fire used conventional AEDs (Stryker LIFEPAK 1000 AED) and we replaced them with AEDs with cprINSIGHT (Stryker LIFEPAK CR2 AED) in 2018. In this study, cases where a LIFEPAK 1000 defibrillator (LP1000) was used in 2016 and 2017 were control cases and cases where a LIFEPAK CR2 AED (LPCR2) was used in 2018 and 2019 were intervention cases. Exclusion criteria were: no AED used before EMS arrival, AED from other source than Amsterdam Police or Amsterdam Fire (e.g. bystander connection of public acces defibrilator), missing AED ECG data and user failure to deliver CPR. The medical ethics review board of the Amsterdam UMC Academic Medical Center (AMC) approved the study, including the use of data of deceased patients. Deferred consent was obtained from all surviving patients.

Conventional algorithm and the cprINSIGHT algorithm

The LP1000 defibrillator used a conventional AED algorithm and analysis that instructs the rescuer to stop chest compressions for heart rhythm analysis every two minutes. The pause in chest compressions was followed by a shock or a no-shock decision (Figure 1). If the device made a shock decision, the AED was charged after which the rescuer was prompted to deliver a shock and after defibrillation to resume CPR. If the decision is no-shock advised, the rescuer was prompted to resume CPR immediately.

By contrast, the LPCR2 AED used the cprINSIGHT algorithm, which analyzes the ECG and removes compression artifacts guided by the transthoracic impedance. Thereafter, it works with the filtered signal, calculating various features and using these measurements to decide. The first analysis in the LPCR2 was a conventional analysis where CPR was interrupted for an analysis. After the first analysis and resumption of CPR, the cprINSIGHT algorithm was activated and subsequent analyses used the cprINSIGHT algorithm. The algorithm started the analysis of the rhythm 30 seconds before the expected end of the 2-minute cycle and classified the rhythm as shockable, not shockable or inconclusive. When the algorithm detected a shockable rhythm the AED was charged while CPR was continued and was ready for defibrillation at the end of the 2-minute cycle. Then the rescuer was prompted to stop CPR, deliver the shock and after defibrillation to resume CPR (Figure 1a). If the algorithm detected a non-shockable rhythm, no voice prompt was given and the rescuer continued CPR without interruption (Figure 1b). If the algorithm result was inconclusive during CPR, the AED prompted for a pause in CPR and used a conventional analysis to reach a decision (Figure 1c).

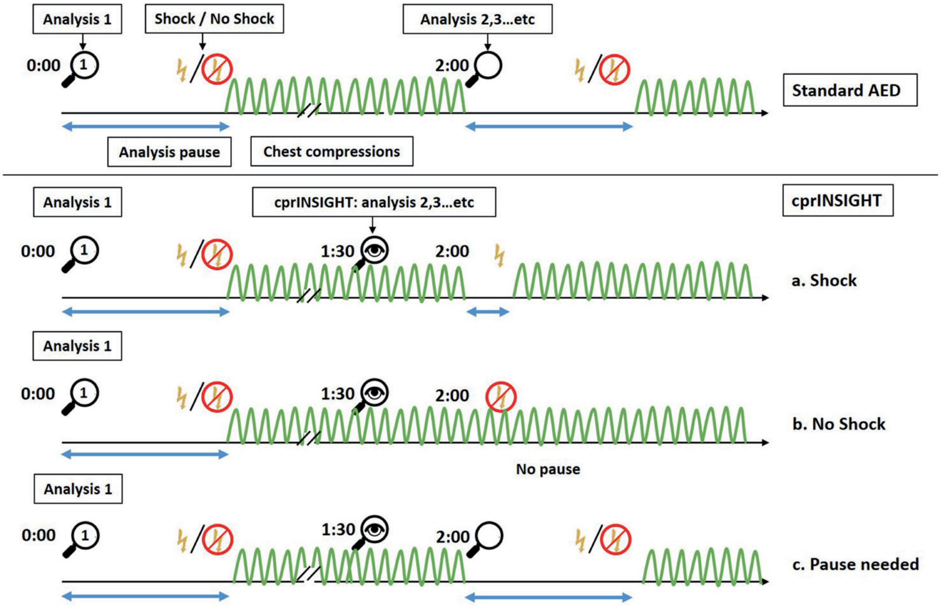

Figure 1: Conventional AED algorithm and cprINSIGHT algorithm. In this figure the green curved line represents chest compressions. Conventional AED: conventional AED algorithm with every 2-minute cycle a pause in chest compressions for heart rhythm analysis and shock or no shock decision. cprINSIGHT: every first analysis is a conventional analysis, analysis 2,3…etc will use the cprINSIGHT algorithm which start 30 seconds before the end of a 2-minute cycle. **a:** cprINSIGHT "shock": analysis during the last 30 seconds of a CPR cycle with a decision during chest compressions, only pause for shock delivery. **b:** cprINSIGHT "no shock": analysis during the last 30 seconds of a CPR cycle with a decision during chest compressions, no pause needed, chest compressions are not interrupted at all. **c:** cprINSIGHT "pause needed": analysis during the last 30 seconds of a CPR cycle, but a shock or no-shock decision during chest compressions could not be made. Then a voice prompt to pause is given and a conventional analysis is done to arrive at a shock or no shock decision.

Data collection and analysis

The AED data were collected either by direct downloading of the AED ECG recording from its memory (LP1000) or by wireless transmission of the data to the ARREST study center (LPCR2). The ECG data were stored and reviewed using CODE-STAT software (Version 10, Stryker Emergency Care, Redmond. USA). Shockable rhythms included ventricular fibrillation (VF) and ventricular tachycardia (VT) with a QRS complex >160msec, no clear p-waves and a ventricular rate of 120/min or higher. VF included both coarse VF (≥200µV) and fine VF (amplitude of 80µV up to 200µV). Non-shockable rhythms included asystole and organized rhythm. Study physicians (CG and RWK) reviewed all AED decisions and

associated rhythms. The AED decision was classified as correct or incorrect, based on a visual inspection of the unfiltered AED ECG segments with ongoing chest compressions and during pauses for ventilations before and after each decision.
For both the LP1000 and LPCR2 cases the sensitivity and specificity were calculated for all analyses after the first analysis. Sensitivity was defined as the number of correct shock decisions divided by the total number of shockable rhythms. Specificity was defined as the number of correct no shock decision divided by the total number of non-shockable rhythms. CCF and pre-shock pause duration were calculated for all LP1000 and LPCR2 cases using the transthoracic impedance signal to identify when chest compressions were administered.[15] CCF was defined as the proportion of time devoted to chest compressions during each 2-minute cycle. The 2-minute cycle began at the start of CPR after an analysis and ended with the start of CPR after the next analysis, which was also marked as the start for the next 2-minute cycle. When cprINSIGHT made a no shock decision, chest compressions were not interrupted and the 2-minute cycle ended at the moment the no shock advice was annotated by the system, which was also marked as the start for the next 2-minute cycle (Figure 1b). A pre-shock pause was defined as the interval between the last chest compression before the delivery of the defibrillation shock and the moment of the defibrillation shock. A post-shock pause was defined as the interval between a shock and resumption of CPR. CCFs and pre-shock pauses were analyzed for all 2-minute cycles and shocks starting with the first chest compression after the first analysis to the end of the last full cycle before the disconnection of the AED.

Outcome

The endpoints of the study were the sensitivity and specificity of the cprINSIGHT algorithm, the proportion of shock and no shock decisions during chest compressions, chest compression fraction and pre-shock pause.

Statistical analysis

Categorical variables were presented as percentages, and continuous variables as mean and standard deviation or as the median and interquartile range (IQR) depending on the data distribution. Chi-square statistics, unpaired t-test or Mann-Whitney U test were used when appropriate. Sensitivity and specificity were calculated for all LP1000 and LPCR2 cases using all analyses of each patient, excluding the first analysis (analysis 1, in both AEDs, was a conventional analysis). In the LPCR2 cases, sensitivity and specificity were also calculated for those analyses with a cprINSIGHT decision during CPR without the need for a pause. The analysis accounted for clustering of multiple observations per patient, using the analysis technique of Zhou, that accurately estimates the sensitivity, specificity and the one-sided 90% lower confidence limit (LCL).[16, 17] For the comparison of the sensitivity, specificity, CCF and pre-shock pause duration between the intervention LPCR2 AEDs with cprINSIGHT and control LP1000 AEDs, generalized estimating equations (GEE) was used to estimate the response, taking into account multiple analyses per patient. Analysis of CCF and pre-shock pauses included analyses where cprINSIGHT needed a pause and a conventional analysis was done. Statistical analyses were performed using IBM SPSS statistics 25 (IBM Corporation, Armonk, NY)

Results

In the control period, CPR was started in 1361 patients and during the intervention period in 1183 patients. Of these, 497 control cases (37%) and 439 intervention cases (37%) had an AED connected by police or firefighters. Excluding the cases with missing AED ECG or user failure to deliver CPR, 465 control cases and 425 intervention cases were included for analysis (Figure 2). The baseline characteristics of these patients are shown in Table 1. While the AED was connected, 418 control cases (90%) and 365 intervention cases (86%) had 2 or more analyses. The number of cases which had 2, 3, 4 or ≥5 AED analyses during connection duration are shown in eFigure1.

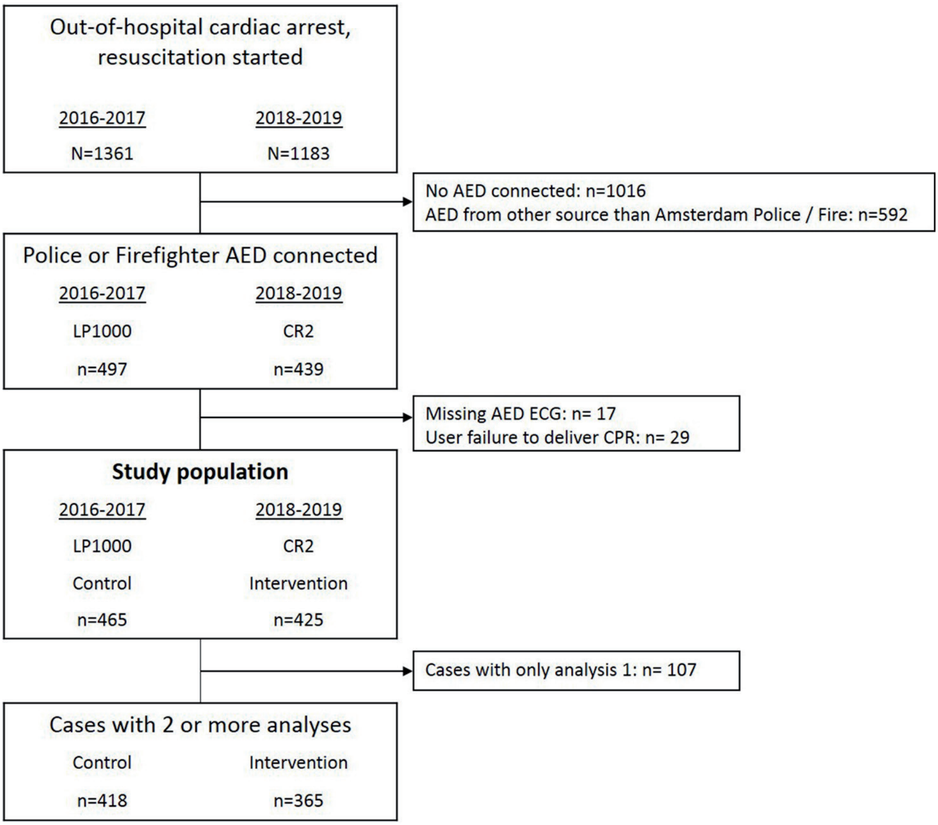

Figure 2: Flowchart of patient inclusion and exclusion

Table 1. Baseline characteristics of OHCA patients with an AED connected

	2016-2017 Control LP1000 N=465	2018-2019 Intervention LPCR2 N=425	*P*-value
Pre-OHCA factors			
Age, years, median (IQR 25,75)	67 (55,77)	66 (52,75)	0.6
Male n (%)	318 (68%)	305 (72%)	0.3
Pacemaker, n (%)	9 (2%)	14 (3%)	0.2
Resuscitation parameters			
First monitored rhythm, n (%)			0.8
VF [coarse & fine VF]	143 (31%)	133 (31%)	
Pulseless VT	3 (1%)	1 (1%)	
Organized rhythm	113 (24%)	101 (24%)	
Asystole	206 (44%)	190 (44%)	
Shockable rhythm at any time, n (%)	155 (33%)	149 (33%)	0.9
Time intervals			
Call to connection of AED, min, mean (SD)	8 (3)	8 (4)	0.4
AED connection to first defibrillation, sec, median (IQR 25,75)*	20 (17, 24)	19 (17,20)	0.009
Total AED connection time, min, median (IQR 25,75)	5 (3,7)	5 (3,6)	0.3

*In case of AED defibrillation
VF - ventricular fibrillation; VT - ventricular tachycardia; AED – Automated External Defibrillator; IQR – Inter-quartile range; SD - standard deviation;

Accuracy of the intervention AED

The 418 control cases and 365 intervention cases with 2 or more analyses resulted in a total of 852 control analyses and 726 intervention analyses. The sensitivity of the control AED was 99.3% (LCL 98.5%) and the specificity was 98.7% (LCL 98.2%). The intervention AED had a sensitivity of 95.5% (LCL 93.1%) and a specificity of 98.2% (LCL 97.5%). The sensitivity and specificity of the control AED and intervention AED were not significantly different (Figures 3a and 3b). This included all analyses except analysis 1, irrespective if the decision was by cprINSIGHT during chest compressions or a pause was needed for a conventional analysis. Table 2 shows the accuracy for the shockable rhythms (VF and VT separately) and non-shockable rhythms (organized rhythm and asystole separately) for the control AED (Table 2a) and intervention AED (Table 2b). For the intervention AED, the sensitivity for VF only was 95.4% (LCL 92.9%) and the specificity was 99.5% (LCL 98.9%) for organized rhythm only and 97.5% (LCL 96.5%) for asystole only. The sensitivity and specificity of the cprINSIGHT decision during chest compressions are shown in eTable 2.

Table 2a. Accuracy of control (LP1000 AED) all analyses (excl. analysis 1)

	Patients	Analyses	Shock advised	No Shock advised	Accuracy	90% LCL
Shockable rhythm					**Sensitivity**	
VF [coarse & fine VF]	96	146	145	1	99,3%	98,4%
Pulseless VT	4	4	4	0	100%	47,3%
Non shockable rhythm					**Specificity**	
Organized rhythm	139	211	1	210	99,5%	98,9%
Asystole	238	491	8	483	98,4%	97,6%

VF - ventricular fibrillation; VT – ventricular tachycardia; LCL - lower confidence limit

Table 2b. Accuracy of intervention (LPCR2 AED) all analyses (excl. analysis 1)

	Patients	Analyses	Shock advised	No Shock advised	Accuracy	90% LCL
Shockable rhythm					**Sensitivity**	
VF [coarse & fine VF]	82	110	105	5	95,4%	92,9%
Pulseless VT	2	2	2	0	100%	22,4%
Non shockable rhythm					**Specificity**	
Organized rhythm	130	216	1	215	99,5%	98,9%
Asystole	209	398	10	388	97,5%	96,5%

VF - ventricular fibrillation; VT – ventricular tachycardia; LCL - lower confidence limit

In 505 (70%) of the 726 intervention analyses, a decision was made during chest compressions. When the patient's rhythm was VF, the cprINSIGHT algorithm reached a decision without the need for a pause in 95 (86%) of 110 shockable rhythm analyses. For non-shockable rhythms, the cprINSIGHT algorithm reached a decision without a need for a pause 78% of the time for organized rhythms and 62% for asystole. The decision rate per AED analysis and proportions of rhythms with a decision during chest compressions for each AED analysis separately are shown in eFigure 2 and eTable 1.

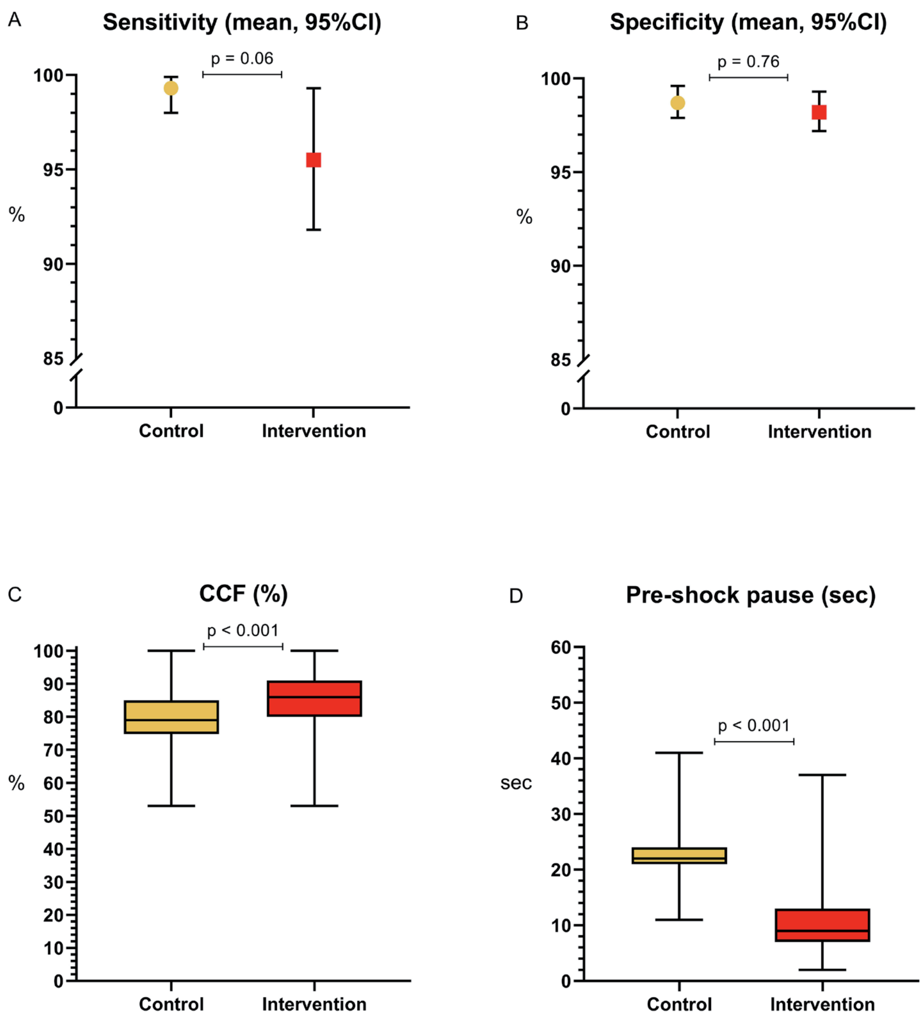

Figure 3. Overall comparison control LP1000 AED and intervention LPCR2 AED (excl. analysis 1)

Panel A: Comparison of sensitivity between control LP1000 AED and intervention AED LPCR2, mean sensitivity (all VF and VT) with 95% Confidence Interval (CI). **Panel B:** Comparison of specificity between control LP1000 AED and intervention AED LPCR2, mean specificity (organized rhythm and asystole) with 95% Confidence Interval (CI).**Panel C:** Comparison of chest compression fraction (CCF) between control LP1000 AED and intervention AED LPCR2, boxplot median percentage with IQR and lowest and highest values. **Panel D:** Comparison of pre-shock pause between control LP1000 AED and intervention AED LPCR2, boxplot indicates median (seconds) with IQR and lowest and highest values.

Chest compression fraction and pauses in compressions

Taking into account the multiple analyses per patient, intervention cases had a significantly higher median CCF of 86% (IQR 79, 92) compared to 80% (IQR 73, 86) in control cases (Figure 3c and Table 3). CCF was ≥80% in 71% of intervention cases and 50% of control cases (eFigure 3). In 158 control analyses and 118 intervention analyses, a shock was advised. The median pre-shock pause of 8 seconds (IQR 7, 11) in intervention cases was significantly shorter compared to 22 seconds (IQR 20, 24) in control cases (Figure 3d and Table 3). The pause associated with non-shockable rhythms was significantly shorter in intervention cases than control cases (Table 3). The comparison between intervention and control cases of analysis 2, 3, 4 and ≥5 separately are shown in eTable 3.

Table 3. Chest compression fraction and pauses in control and intervention cases: clustered analysis

	2016-2017 Control LP1000 N=418 cases / 852 analyses	2018-2019 Intervention LPCR2 N=365 cases / 726 analyses	*P*-value for clustered analysis
Chest compression fraction, analyses, n	**852**	**726**	
Chest compression fraction, median, IQR	80 (73,86)	86 (79,92)	<0.001
Chest compression fraction, ranges, n (%)			<0.001
<60%, n (%)	29 (3%)	6 (1%)	
≥60 – 70%, n (%)	106 (13%)	26 (4%)	
≥70 – 80%, n (%)	290 (34%)	169 (24%)	
≥80 – 90%, n (%)	310 (36%)	268 (37%)	
≥90, n (%)	117 (14%)	247 (34%)	
Shockable rhythm, analyses, n	**158**	**118**	
Peri-shock pause, seconds, median (IQR 25,75)*	25 (22,29)	12 (10,16)	<0.001
Pre-shock pause	22 (20,24)	8 (7,11)	<0.001
Post-shock pause	3 (2,5)	4 (3,5)	0.5
Non-shockable rhythm, analyses, n	**702**	**614**	
Analysis pause, seconds, median (IQR 25,75)	11(10,14)	0 (0, 10)	<0.001

*In case of AED defibrillation
IQR – Inter-quartile range

5

Discussion

Our study showed that in OHCA patients who were treated with an AED with the cprINSIGHT algorithm that has the ability to perform rhythm analysis during chest compressions, a decision could be made during chest compressions over two-third of analyses. When the device reached a shock or no shock decision, the accuracy was high with high sensitivity for shockable rhythms and high specificity for non-shockable rhythms. Furthermore, compared to a conventional AED the use of this new algorithm led to a significantly higher chest compression fraction and shorter pre-shock pauses.

With a LCL of 93.1% for the sensitivity of 95.5% and a LCL of 97.5% for the specificity of 98.2%, the intervention AED with the cprINSIGHT algorithm meets the performance goals of the AHA recommendations for arrhythmia analysis accuracy in AEDs, accounting for all analyses with or without need for an analysis pause.[18] The cprINSIGHT algorithm demonstrates that rhythm analysis during chest compressions is feasible and does not compromise the performance goals. These performance goals were set for artifact-free analyses and coarse VF only. Although the survival prognosis of fine VF (amplitude 80-200 µV) is less favorable than of coarse VF (amplitude >200 µV), guidelines do not distinguish fine VF from coarse VF in their recommendation to shock. Fine VF can be more difficult to identify than coarse VF. Therefore, incorporating both coarse VF and fine VF in the decision to defibrillate makes the adequate performance of this analysis during chest compressions even more valuable.

Our results show a significant increase in CCF, a significant decrease in pauses for non-shockable rhythms and a significant decrease in pre-shock pause duration in cases where an AED with cprINSIGHT was used compared to cases where a conventional AED was used. Observational studies have investigated the associations between CCF, pre-shock pause duration and survival. Studies on the association between CCF and survival show inconsistent results. Some studies have shown that in both patients with shockable rhythms and non-shockable rhythms, a higher CCF was independently associated with better survival,[19, 20] while other studies did not show such an association between CCF and survival.[21-23] Studies on pre-shock pause found that in patients with a shockable rhythm, the duration of the pre-shock pause was associated with return of spontaneous circulation (ROSC), showing that the probability of ROSC declined when the duration of pre-shock pauses increased, while shorter pre-shock pauses were associated with better survival.[10, 24-26] The increase in CCF (86% vs 80%) and the decrease in pre-shock pause (8 sec vs 22 sec) as found in our study can be expected to be favorable for survival, but that endpoint was not the objective of our study.

Previous studies have shown the potential benefit of different algorithms in analyzing the ECG during chest compressions in test datasets and simulated OHCA but clinical experience on OHCA patients with these algorithms is not yet reported.[27-31] Data have been published on two other algorithms designed for analysis during chest compressions in AEDs. When tested with a data set of ECG segments, the ADC-FR algorithm always included a compression pause of at least 3 seconds for reconfirmation and had a 95% sensitivity and a 99% specificity. It could reach a decision with a 3-second pause in 84% of cases but in the other 16% of cases, the reconfirmation analysis needed to be extended up to 9 seconds.[30] In dataset testing, the ATC algorithm could reach a shock decision without the need for an additional chest compression-free analysis with a sensitivity of 71%. In the remainder of ECG segments, a conventional analysis with interruption of chest compressions was required after which the sensitivity was 94% and the specificity 99.5%.[31] Our study is the first clinical study on a new algorithm installed in an AED and used in OHCA, making the results representative of the clinical performance during AED use by rescuers.

Our study shows that in 30% of cprINSIGHT analyses a pause in chest compressions and conventional analysis was needed to reach a decision. The proportion of cases where an interruption of chest compressions and conventional analysis was needed, was the highest in case of asystole (38%) followed by organized rhythm (22%) and lowest in case of VF (12%). For patients with a pacemaker and pacemaker spikes on the ECG (irrespective of the underlying rhythm) the cprINSIGHT algorithm is programmed to have a pause in chest compressions and a conventional analysis to reach a decision. This occurred in 14 cases (3%) of our intervention study population. Therefore, the current limitations of cprINSIGHT mainly affect cases with non-shockable rhythms, mostly asystole.

Limitations

Our study has some limitations. First, although the 90% lower confidence limit of both sensitivity and specificity reached the performance goal, the 110 VF analyses in which the intervention AED made a decision is less than the minimum test sample size of 200 analyses mentioned in the recommendations.[18] However, the most relevant measure is the lower confidence limit, which already exceeds the requirements and it is very unlikely that enlarging the study size would have widened the confidence interval and lowered the LCL. It was impossible to collect the required 50 VT cases in the clinical context of OHCA. VT is so infrequent, that it would have required a 50 times larger patient sample and an unrealistic study duration. Second, the analysis of CCF and pre-shock pause duration involved comparing subsequent periods of AED use, in which unknown factors could have influenced the performance of the users. This is unlikely, as the same users (Police and Firefighters) and in the same region (Amsterdam) used the AEDs and no protocol change was introduced in the study period. In addition, patient characteristics were not significantly different. Third, in this study, we only compared chest compression fraction and pre-shock pause duration and did not study survival outcomes. To compare outcome measures such as ROSC and survival a very different study design, preferably a randomized study, and far greater numbers of patients would be required. Furthermore, it has to be taken into account that the use of an AED with improved technology is only one link in the chain of survival of OHCA

Conclusion

In OHCA cases, an AED with a new AED algorithm could analyze the ECG during chest compressions in more than two-third of rhythm analyses with an accuracy comparable to conventional AEDs. Compared to conventional AEDs, this new algorithm leads to higher CCF and a shorter pre-shock pause.

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Conflict of interest statement

CG was supported and received a speaker's fee from Stryker. RES, DP and FWC were employees of Stryker Emergency Care. RWK was the recipient of the funding for maintaining the ARREST database. Stryker supplied the LPCR2 AEDs on loan and replacement of batteries and electrodes for the duration of the study.

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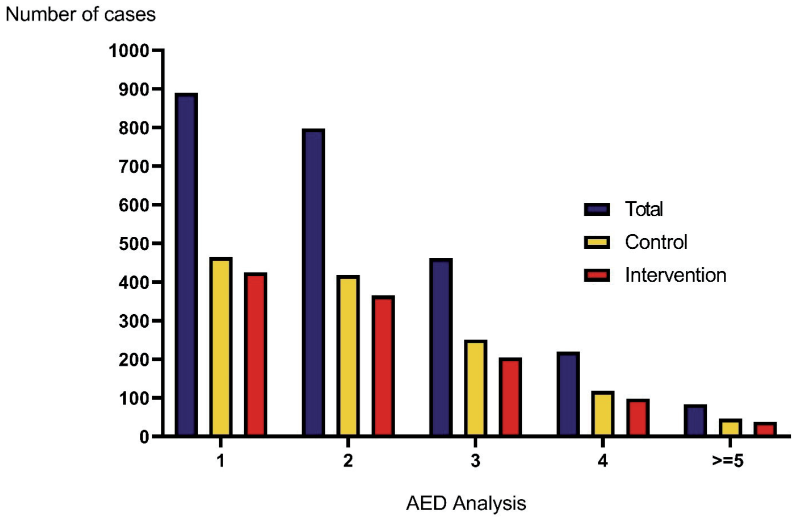
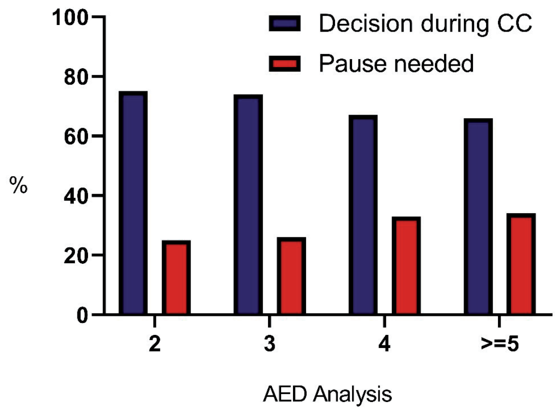
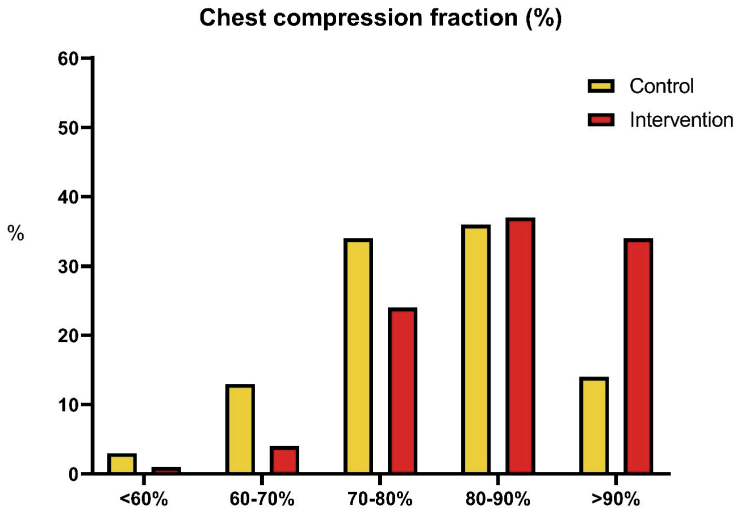
Supplementary materials



eFigure 1. Number of cases per analysis



eFigure 2. Intervention LIFEPAK CR2 AED cprINSIGHT decision rate without and with pause



eFigure 3: Chest compression fraction intervals

eTable 1. Intervention LIFEPAK CR2 AED proportion of decisions during chest compressions

	Analysis 2 n=365	Analysis 3 n=205	Analysis 4 n=98	Analysis ≥5[a] n=37
Monitored rhythm, n (%)				
VF [coarse & fine VF]	75 (21%)	22 (11%)	9 (9%)	4 (7%)
Decision during CC	63 (84%)	20 (91%)	8 (89%)	4 (100%)
Pause needed	12 (16%)	2 (9%)	1 (11%)	0 (0%)
Pulseless VT	1 (1%)	1 (1%)	-	-
Decision during CC	0 (0%)	1 (100%)	-	-
Pause needed	1 (100%)	0 (0%)	-	-
Organized rhythm	100 (27%)	64 (31%)	29 (30%)	23 (40%)
Decision during CC	78 (78%)	51 (80%)	25 (86%)	15 (65%)
Pause needed	22 (22%)	13 (20%)	4 (14%)	8 (35%)
Asystole	189 (51%)	118 (57%)	60 (61%)	31 (53%)
Decision during CC	125 (66%)	71 (60%)	31 (52%)	19 (61%)
Pause needed	64 (34%)	47 (40%)	29 (48%)	12 (39%)

[a] the 37 cases with 5 or more analyses included a total of 58 analyses
VF - ventricular fibrillation; VT - ventricular tachycardia; CC - Chest compressions

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eTable 2. Accuracy of cprINSIGHT algorithm with a decision during chest compressions

	Analyses (n)	Correct advice (C)	Incorrect Advice (I)	Pause needed for analysis (P)	Proportion decided during CC(C+I)/n	Accuracy decision during CCC/(C+I)	90% LCL of accuracy decision during CC
Shockable rhythm						**Sensitivity**	
VF [coarse & fine VF]	110	90	5	15	86%	94,7%	91,9%
Pulseless VT	2	1	0	1	50%	100%	5,5%
Non shockable rhythm						**Specificity**	
Organized rhythm	216	169	0	47	78%	100%	99,2%
Asystole	398	240	6	152	62%	97,6%	96,3%

VF - ventricular fibrillation; VT - ventricular tachycardia; CC - Chest compressions; LCL - lower confidence lim

eTable 3. Comparison of control (LIFEPAK 1000 AED) and intervention (LIFEPAK CR2 AED) cases per analysis

	Analysis 2		Analysis 3		Analysis 4		Analysis ≥5	
	Control N=418	**Intervention N=365**	**Control N=251**	**Intervention N=205**	**Control N=118**	**Intervention N=98**	**Control N=46**	**Intervention N=37**
Monitored rhythm, n (%)								
VF [coarse & fine VF]	92 (22%)	75 (20%)*	40 (16%)	22 (11%)*	10 (8%)	9 (9%)*	3 (6%)	3 (8%)*
Pulseless VT	2 (1%)	1 (1%)*	-	1 (1%)*	1 (1%)	-	-	-
Organized rhythm	107 (25%)	100 (27%)*	63 (24%)	64 (31%)*	30 (26%)	29 (29%)*	10 (22%)	12 (32%)*
Asystole	217 (52%)	189 (52%)*	148 (59%)	118 (57%)*	77 (65%)	60 (61%)*	33 (72%)	22 (60%)*
Peri-shock pause, seconds, median (IQR 25,75)								
Pre-shock pause	22 (20,24)	8 (6,12)	22 (21,23)	8 (7,11)	23 (22,26)	8 (7,10)	20 (17,23)	6 (4,8)
Post-shock pause	3 (2,5)	4 (3,5)	3 (2,5)	3 (2,5)	8 (8,10)	4 (3,6)	9 (8,11)	4 (2,6)
Analysis pause, seconds, median (IQR 25,75)	12 (10,14)	0 (0,10)	12 (10,14)	0 (0,9)	11 (10,14)	0 (0,12)	11 (9,13)	0 (0,9)
Chest compression fraction								
Median, IQR	79 (72,85)	86 (80,93)	80 (73,85)	85 (77,91)	81 (76,85)	86 (78,91)	84 (77, 90)	87 (83,91)
<60%, n (%)	18 (4%)	3 (1%)	6 (2%)	3 (1%)	4 (3%)	2 (2%)	0 (0%)	0 (0%)
≥60 – 70%, n (%)	58 (14%)	15 (4%)	35 (14%)	6 (3%)	10 (9%)	3 (3%)	1 (2%)	2 (5%)
≥70 – 80%, n (%)	148 (35%)	70 (19%)	83 (33%)	64 (32%)	40 (34%)	26 (26%)	14 (31%)	4 (11%)
≥80 – 90%, n (%)	136 (33%)	140 (38%)	95 (38%)	67 (33%)	53 (45%)	36 (37%)	18 (40%)	18 (49%)
≥90, n (%)	58 (14%)	134 (38%)	31 (12%)	62 (31%)	11 (9%)	31 (32%)	12 (27%)	13 (35%)

* in comparison with control p>0.05

VF - ventricular fibrillation; VT - ventricular tachycardia; AED – Automated External Defibrillator; IQR – Inter-quartile range

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PART 3

EMS decision when to transport with ongoing CPR

CHAPTER 6

Time of on-scene resuscitation in out-of-hospital cardiac arrest patients transported without return of spontaneous circulation.

C. de Graaf, S.G. Beesems, R.W. Koster

Resuscitation. 2019; 138: 235-242

Abstract

Background

In out-of-hospital cardiac arrest (OHCA), return of spontaneous circulation (ROSC) on scene occurs only in a minority of patients. The optimal duration of resuscitation on scene before transport with ongoing cardiopulmonary resuscitation (CPR) is unknown.

Purpose

To determine the time of resuscitation on scene ('time on scene') and survival in patients transported with ongoing CPR in the Netherlands.

Methods

Data on OHCA patients (>18 years) without ROSC on scene, where resuscitation was started between January 1, 2012 and December 31, 2016 in the Amsterdam Resuscitation Study (ARREST) database were analyzed. Time on scene was related to 30-day survival.

Results

Of the 5871 OHCA patients where resuscitation was started, 2437 did not achieve ROSC on scene. Of these, 655 patients were transported with ongoing CPR and 606 (93%) had complete rhythm data. At the moment of transport, 199 (33%) patients had a shockable rhythm, 299 (49%) pulseless electrical activity (PEA) and 108 (18%) asystole as rhythm. Twenty-nine patients (4%) were alive at 30 days. Patients who survived 30 days had a higher proportion of a shockable first monitored rhythm (89% vs. 52%, $p < 0.001$). Survivors had a significantly shorter time on scene (20 min vs. 26 min, $p = 0.004$), with the highest survival rate (8%) in patients transported within 20 minutes. In a multivariable model time on scene (OR 0.94; 95%CI 0.89 - 0.99) was independently associated with 30-day survival.

Conclusion

In OHCA patients transported with ongoing CPR the survival rate significantly declines when time on scene increases.

Introduction

In out-of-hospital cardiac arrest (OHCA) patients, advanced life support does result in return of spontaneous circulation (ROSC) on scene in a minority of patients, ranging between 15% and 45%. [1-5] Survival of patients transported with ongoing CPR is low, but there is sufficient evidence that transport is not futile (above a 1% futility rate[6]) and should be considered.[1,4,7] While the termination of resuscitation guidelines apply to approximately 30% of patients with OHCA, many patients that do not meet these criteria, do not achieve ROSC on scene.[8,9] Positive patient and process characteristics associated with survival to hospital discharge in patients transported with ongoing CPR are bystander-witnessed arrest, initial shockable rhythm, public location and emergency medicals services (EMS) witnessed arrest.[1,3,5]

What is the optimal moment to decide to initiate transport with ongoing CPR? According to the European Resuscitation Council (ERC) guidelines in 2015 the decision to transport with ongoing CPR should be weighed after 10 minutes of passed on-scene resuscitation, however this time is not supported with data.[10] The American Heart Association (AHA) guidelines of 2010 recommend optimizing care on scene to achieve ROSC rather than transport with ongoing CPR, but give no specific guidance when to transport to the hospital if ROSC is not achieved.[11] The AHA guideline is not updated on this topic in 2015. Currently, it is unclear at what time in the resuscitation process the decision to transport a patient with ongoing CPR should be made. Emergency medical services (EMS) have to take in account the risk of transporting an unstable patient in a moving vehicle who may have achieved ROSC if resuscitation efforts on scene had continued longer. The aim of this study is to determine the relation between time on scene and survival in patients transported with ongoing CPR, in a system in which extracorporeal cardiopulmonary resuscitation (ECPR) was not yet implemented.

Methods

Study setting and design

This study was performed using data from the Amsterdam Resuscitation Study (ARREST). The ARREST study is an ongoing prospective registry of all-cause OHCA in North-Holland, a province of the Netherlands. The registry was established to identify the determinants of outcome of OHCA.[12,13] The study region covers an area of 2404 km^2 and had a population of 2.8 million in 2015.[14] All adult OHCA patients (>18 years) without ROSC on scene, between January 1, 2012, to December 31, 2016, were included. Exclusion criteria were (transient) ROSC prior to transport and unknown survival status. Patients with complete data considering the first monitored rhythm, the rhythm at the start of transport and rhythm at hospital arrival were analyzed to identify the different rhythms and survival. The medical ethics review board of the Amsterdam UMC, Academic Medical Center, approved the study (nr. W18_231 # 18.276)

EMS system in the study region

In a medical emergency, the national emergency number will be dialed and if the dispatcher suspects an OHCA, two EMS teams are dispatched. Each ambulance is equipped with a manual defibrillator and manned with a driver, who is qualified to perform Basic Life Support (BLS), and a paramedic, who is qualified to perform Advanced Life Support (ALS). In addition, first responders, equipped with an automated external defibrillator (AED), are dispatched. These first responders are firefighters, police officers and/or citizen-responders, trained in BLS and AED use. Also, many public areas in the study region have AEDs and every individual in the study region is allowed to use these AEDs.
In the study region three dispatch centers participated, each with one EMS agent. The EMS follows a national protocol for cardiac arrest based on the European guidelines.[15,16] In the national protocol it is stated, when a patient despite resuscitation efforts does not achieve ROSC, EMS can consider termination of resuscitation after 20 min of ALS in case of a non-shockable rhythm and in the absence of a reversible cause. Early transport is to be considered early in the process e.g., after 10 min of ALS without ROSC in patients with ventricular fibrillation (VF), ventricular tachycardia (VT) or treatable cause, but at what precise moment a decision to transport with ongoing CPR should be initiated is not described in the national protocol and the ERC Guidelines, nor what specific criteria are involved in such a decision. Physicians are not part of the standard dispatched EMS team and the paramedic is qualified and legally allowed to make termination of resuscitation decisions without consulting a physician in the pre-hospital setting. During the study period, in two of the three participating regions a mechanical CPR device was available in the ambulance. There were no hospitals in the region that used ECPR as a treatment strategy in OHCA patients.

Data collection

If a resuscitation is attempted by EMS, EMS routinely sends the continuous electrocardiography (ECG) from their manual defibrillator and EMS run report to the ARREST study center. In addition, the paramedic also answers a pre-determined set of questions considering specifics of the patient and condition before and during transport. If an AED was connected before the ambulance defibrillator, ARREST study personnel visited the AED site shortly after OHCA to collect the AED ECG recording. The ECG from the EMS manual defibrillator and AEDs were stored and analyzed with dedicated software. Clock drift of defibrillators and AEDs was corrected to standardized times for each recording. Data were registered using the Utstein templates for resuscitation registries.[17] Data from the EMS manual defibrillator and AED ECG were analyzed to document the first monitored rhythm, the rhythm at moment of transport, time of the first defibrillation and time of first mechanical CPR compression (if mechanical CPR was used).

Time intervals and definitions

Time-stamped data on emergency call at dispatch center, EMS arrival on scene, EMS departure from scene and arrival at the emergency department (ED) were collected to create time intervals. EMS arrival on scene was defined as the moment the EMS manual defibrillator was connected to the patient. The 'time on scene' of EMS was the interval between EMS arrival on scene and departure of the ambulance from the scene. In cases of EMS witnessed arrests, 'time on scene' was the interval between collapse and departure of the ambulance from the scene. If the resuscitation was terminated on scene, 'time on scene' was the interval between EMS arrival and disconnection of the EMS manual defibrillator at the moment of termination. 'The 'total prehospital time' was the time between the emergency call at the dispatch center and the arrival at the ED. Information considering (transient) ROSC was collected from the EMS report and defined as: a palpable pulse or a measurable blood pressure.

Outcome

The outcome of this study was overall 30-day survival, based on information from the National Civil Registry.

Statistical analysis

Categorical variables were presented as percentages and continuous variables as mean and standard deviation (SD) or as median and interquartile range (IQR) depending on the data distributions. Chi-square statistics were used to compare categorical data. For continuous data unpaired t-test or Mann-Whitney U test was used when appropriate. A multivariable logistic regression model was used to investigate independent associations between time on scene and 30-day survival. A stepwise-forward approach was used with variables significantly associated in univariate analysis (p-value < 0.05). In the model, the number of events per variable was 10.[18] Consequently, in this study a maximum of 3 variables were allowed in the model. Associations were reported as odds ratio with 95% confidence intervals (CI) and associated p values. The Hosmer-Lemeshow test was used to test the model for goodness of fit. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics 24 (IBM Corporation, Armonk, NY).

Results

Out of 12348 patients with suspected OHCA in the study period, 5871 had attempted resuscitation by EMS. Of these, 3231 patients did not achieve ROSC on scene of which, after exclusion, 2437 patients were included for analysis. In 1782 patients the resuscitation was terminated on scene and 655 patients were transported with ongoing CPR (Figure 1).

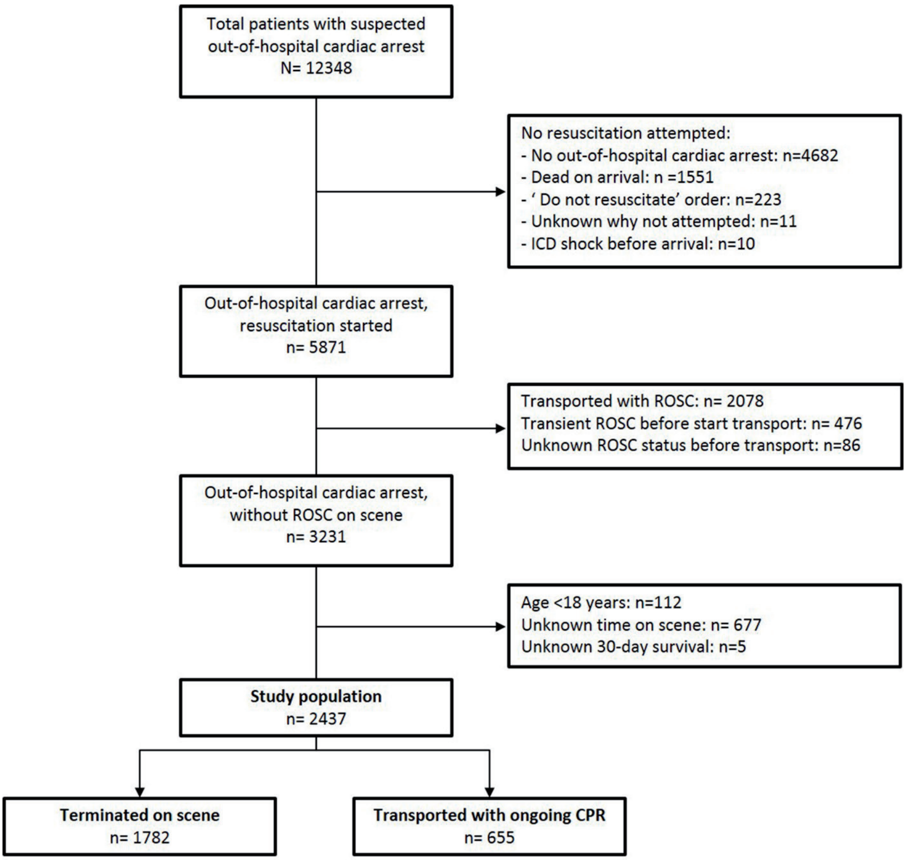

Figure 1: Flowchart of patient inclusion. In 5871 cases EMS personnel attempted to resuscitate of which 3231 without ROSC on scene, including 2427 patients aged ≥18 years with complete survival data (died on scene: n=1782; transported with ongoing CPR: n=655). Years 2012-2016 in the Netherlands

Baseline patient and process characteristics

Patient and process characteristics of patients without ROSC on scene are shown in Table 1. Patients who were transported with ongoing CPR were significantly younger, had a higher proportion of shockable first monitored rhythm, had their arrest more often in public locations, and the arrest was more often witnessed, compared to patients without ROSC and a resuscitation that was terminated on scene. In patients who were not transported, the median time on scene before termination of resuscitation was 23 (IQR 17, 28) minutes. Patients transported with ongoing CPR had a median time on scene of 25 (IQR 19, 32) minutes before the start of transport. The regional EMS agencies with mechanical CPR devices utilized it in 83% of the cases, with a median connection time of 3 minutes after EMS arrival.

First monitored rhythm, rhythm at moment of transport and rhythm at ED arrival

Of all patients transported with ongoing CPR, 606 (93%) had complete data on the time of first monitored rhythm, the rhythm at moment of transport and rhythm at ED arrival. The rhythms at different stages in the resuscitation are illustrated in Figure 2. At the moment of transport, 199 (33%) patients had VF/VT, 299 (49%) pulseless electrical activity (PEA) and 108 (18%) asystole as rhythm. At ED arrival 25 patients (4%) had ROSC, leaving 113 (19%) with VF/VT, 324 (53%) with PEA and 144(24%) with asystole.

Outcome

Of the 655 transported patients, 544 died in the emergency room, 111 (17%) were admitted to the hospital and 29 (4%) survived 30 days. Patient and process characteristics of survivors vs non-survivors are shown in Table 2. Patients who survived 30 days had a higher proportion of a shockable first monitored rhythm (89% vs. 52%, $p < 0.001$) and a higher proportion of shockable rhythm at moment of transport (63% vs.31%, $p = 0.001$) compared to patients who died. Figure 2 shows the survival within the rhythm groups and corresponding rhythms of patients at the time of first monitored rhythm, the moment of transport and ED arrival. During transport 25 of 606 (4%) patients achieved ROSC, and 44% of these patients survived. In patients, transported with ongoing CPR, at every time point a shockable rhythm resulted in the highest survival, 7% at moment of first monitored rhythm, 8% at start of transport and 6% at ED arrival respectively. PEA at the moment of first monitored rhythm was associated with a survival of 1% and a survival of 3% at moment of transport and ED arrival. None of the patients with asystole at any time point survived.

Table 1. Baseline characteristics of OHCA patients who died on scene and patients transported with ongoing CPR

	No ROSC and died on scene N=1782	No ROSC and transported N=655	p-value	Missing N (%)
Pre-OHCA factors				
Age, years, mean (SD)	68 (15)	63 (15)	<0.001	-
Sex, n (%)			<0.001	-
Male	1193 (67%)	518 (79%)		
Female	589 (33%)	137 (21%)		
Resuscitation parameters				
First monitored rhythm, n (%)*			<0.001	38 (1.6%)
Shockable (VF/VT)	236 (13%)	345 (54%)		
Not shockable	1524 (87%)	294 (46%)		
Presumed cause, n (%)			<0.001	-
Cardiac	1645 (92%)	577 (88%)		
Not cardiac	137 (8%)	78 (12%)		
Location of arrest, n (%)			<0.001	1 (<0.01%)
Residential	1495 (84%)	397 (61%)		
Public	286 (16%)	258 (39%)		
Witnessed arrest, n (%)			<0.001	19 (0.8%)
Not witnessed	826 (47%)	133 (21%)		
EMS witnessed	62 (3%)	87 (13%)		
Bystander witnessed	880 (50%)	430 (66%)		
Bystander CPR, n (%) **			0.89	16 (0.7%)
Bystander CPR	1370 (81%)	452 (81%)		
No Bystander CPR	322 (19%)	109 (19%)		
Time intervals				
Call to first defibrillation, minutes, median (IQR 25,75)***	12 (9,23)	10 (8,17)	<0.001	10 (1.5%)
Response time, minutes, median (IQR 25,75)	12 (10,15)	12 (9,15)	0.002	3 (<0.01%)
Time on scene, minutes, median (IQR 25,75)****	23 (17,28)	25 (19,32)	<0.001	-

CPR-cardiopulmonaryresuscitation;VF/VT-ventricularfibrillation/tachycardia;EMS-emergencymedicalservices;SD-standarddeviation;IQR-inter-quartilerange; ED – emergency department. * in case of EMS witnessed, first monitored rhythm is rhythm at collapse; ** if not EMS witnessed; *** if shockable rhythm
Percentages shown are column percentages

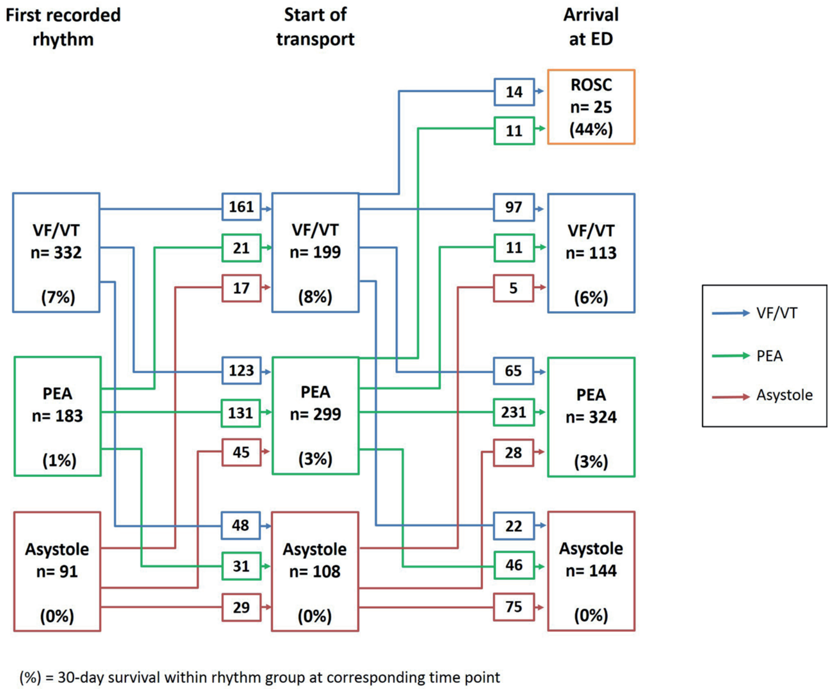

Figure 2. Rhythm and 30-day survival at different time points during resuscitation of patients transported with ongoing CPR. Of the 655 patients transported with ongoing CPR, 609 (95%) had complete data on rhythm at EMS arrival, moment of transport at arrival at ED. The arrows correspond with the number of cases and rhythms indicated with the color. (For example: of the 332 cases with a shockable VF/VT rhythm as first recorded rhythm, 161 also had a shockable VF/VT rhythm at moment of transport). Survival is calculated within each rhythm group at the different time points. (For example: of 199 patients with a shockable rhythm (VF/VT) at moment of transport 16 (8%) survived).

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Table 2. Characteristics of surviving and non-surviving patients transported with ongoing CPR

	Died N=626	30-day survival n=29	*P*-value	Missing n (%)
Age, years, mean (SD)	63 (15)	61 (14)	0.34	-
Sex			0.34	-
Male, n (%)	493 (79%)	25 (86%)		
Female, n (%)	133 (21%)	4 (14%)		
Resuscitation parameters				
First monitored rhythm, n (%)*			<0.001	16 (2.4%)
Shockable (VF/VT)	320 (52%)	25 (89%)		
Not shockable	291 (48%)	3 (11%)		
Presumed cause, n (%)			0.15	-
Cardiac	549 (88%)	28 (97%)		
Not cardiac	77 (12%)	1 (3%)		
Location of arrest, n (%)			0.54	-
Residential	381 (61%)	16 (55%)		
Public	245 (39%)	13 (45%)		
Witnessed arrest, n (%)			0.06	5 (0.8%)
Not witnessed	131 (21%)	2 (7%)		
Witnessed	490 (79%)	27 (93%)		
CPR before EMS arrival			0.10	2 (0.3%)
No bystander CPR	100 (16%)	9 (31%)		
EMS witnessed	83 (13%)	4 (14%)		
Bystander CPR	436 (71%)	16 (55%)		
Rhythm at moment of transport, n (%)			0.001	33 (5.0%)
Shockable (VF/VT)	187 (31%)	17 (63%)		
Not shockable	408 (69%)	10 (37%)		
Time intervals				
Call to first defibrillation, minutes, median (IQR 25,75)**	10 (8,17)	9 (6,12)	0.06	10 (1.5%)
Response time, minutes, median (IQR 25,75)	12 (9,15)	10 (8,14)	0.008	-
Time on scene, minutes, median (IQR 25,75)	26 (20,32)	20 (15,26)	0.003	-
Transport time to ED, minutes, median (IQR 25,75)	8 (5,12)	8 (6,14)	0.45	13 (2.0%)
Total prehospital time, minutes, median (IQR 25,75)	47 (39,55)	45 (36,51)	0.02	13 (2.0%)

CPR - cardiopulmonary resuscitation; VF/VT - ventricular fibrillation/tachycardia; EMS - emergency medical services; SD - standard deviation; IQR - inter-quartile range; ED – emergency department. * in case of EMS witnessed, first monitored rhythm is rhythm at collapse; ** if shockable rhythm
Percentages shown are column percentages

Time on scene and 30-day survival

Patients who survived had a significant shorter time on scene (20 min vs. 26 min, p = 0.003). Figure 3 shows there was a significant trend between time spent on scene and 30-day survival (p for trend = 0.014). In a multivariable model (Table 3) time on scene was independently associated with 30-day survival (OR 0.94; 95%CI 0.89 - 0.99); for every minute longer time on scene before transport, the odds of 30-day survival decreased by 6%. First rhythm VF/VT and response time were also independently associated with 30-

day survival. Rhythm at transport VF/VT was not independently associated with 30-day survival in the multivariable model.

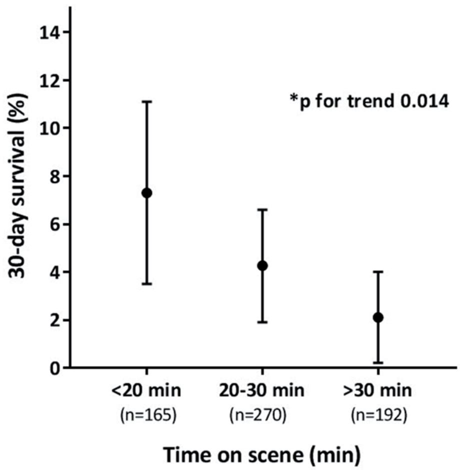

Figure 3. Time on scene intervals and 30-day survival of patients transported with ongoing CPR. Of 178 patients which were transported within 20 minutes of time on scene, 13 (7%) survived. Of the 282 patients transported after 20 to 30 minutes, 12 (4%) survived and of 195 patients transported after 30 minutes, 4 (2%) survived.

Table 3. Multivariable logistic stepwise forward regression of variables associated with 30-day survival

	Unadjusted		Adjusted	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Time on scene	0.93 (0.89 – 0.98)	0.004	0.94 (0.89 – 0.99)	0.02
First rhythm: VF/VT	7.58 (2.26 – 25.36)	0.001	10.52 (2.36 – 43.96)	0.002
Response time	0.88 (0.80 – 0.98)	0.02	0.85 (0.76 – 0.96)	0.007
Rhythm at transport: VF/VT	3.71 (1.67 – 8.26)	0.001	-	-

Hosmer and Lemeshow Test P 0.55:,
OR - odds ratio; CI - confidence interval; ROSC - return of spontaneous circulation; VF/VT - ventricular fibrillation/tachycardia;
[a]: variables put in model stepwise forward: First rhythm, Response time, Time on scene, Rhythm at moment of transport

Discussion

Our study showed that in OHCA patients transported with ongoing CPR the survival rate significantly declined when time on scene increased. Patients with a shockable rhythm as first monitored rhythm and patients with a shockable rhythm at the moment of transport had the highest probability to survive 30 days.

The overall survival of patients transported with ongoing CPR in this study was 4% which is higher than the accepted limit of medical futility.[6] This is in accordance with previous studies which found survival rates of 3.6% and 6%.[1,7] The highest survival rate was found in patients transported within 20 minutes of on-scene resuscitation and patients with a shockable first monitored rhythm. Furthermore, time on scene was independently associated with 30-day survival. This suggests that a shorter time on scene is associated with a higher probability of survival.

In our study besides time on scene, a first monitored rhythm VF/VT was associated with better 30-day survival in the patients transported without ROSC, which is consistent with the guidelines.[10] Yates et al found a survival rate of 1.3% in patients transported with ongoing CPR; all survivors had a shockable first rhythm.[4] Our study showed that patients with a shockable rhythm had the highest chances of 30-day survival with a survival rate at moment of first monitored rhythm and moment of transport of respectively 7% and 8%, but patients with PEA had a survival rate of respectively 1% and 3%. There were no patients with asystole that survived to 30 days.

Although transport should be considered, transporting a patient with ongoing CPR is associated with interruptions in CPR and possible lower survival rate.[19-21] This could be a factor why paramedics may choose to stay longer on scene in non-public locations where moving the patient into an ambulance with ongoing CPR may be challenging. In addition, manual CPR in a moving ambulance reduces the quality of CPR and is potentially harmful to the paramedic.[22,23] To facilitate and support earlier transport in patients without ROSC, the quality of CPR and safety of the paramedics during transport needs to be ensured. The use of mechanical CPR could facilitate this and accelerate the decision to transport with ongoing CPR.[22,24]

At the beginning of resuscitation, it is not known which patients will achieve ROSC and at what time. In our study 5% of all transported patients without ROSC had ROSC at hospital arrival, suggesting they could have achieved ROSC on scene before start of transport if EMS had continued their resuscitation on scene. Earlier studies describe that in OHCA patients, the first 10-15 minutes of standard ALS strategies are most effective and after 15 minutes the probability of survival with good neurologic outcome decreases.[25,26] In our study there were insufficient patients transported within 10 or 15 minutes to analyze the potential benefit of earlier initiation of transport than 20 minutes.

There is a need for novel treatment strategies for patients who do not respond to conventional resuscitation after the first 15 minutes. The use of ECPR in OHCA is a new strategy, which improves the chances of survival in a selected group of OHCA patients.[27] Although randomized studies are lacking, the use of ECPR may be a beneficial therapy, especially when there is a short low-flow time and early ECPR initiation.[28-30] Grunau et al. suggests that the window to transport for ECPR is between 8 to 24 minutes, with 16 minutes as the optimal moment to transport balancing the risks between early transport with ongoing CPR and the possibility of achieving ROSC on scene.[25] Our study suggests that a delay to transport for more than 20 minutes is already associated with lower survival.

Limitations

First, the precise reason for the decision to transport patients with ongoing CPR and terminate CPR in others was not documented. A selection mechanism could be present that our analysis did not detect. Second, this study did not include data considering hospital care and 30-day survival could be affected by interventions such as coronary revascularisation.[31,32] Finally, due to the observational character of this prospective cohort, only an association and not causality between time on scene and survival could be determined. Therefore, our study does not answer the question if an even earlier decision on scene to transport without ROSC would have resulted in even higher survival.

Future research

It remains unclear why a patient is transported with ongoing CPR in some situations, but the resuscitation is terminated in others. Future qualitative studies will explore medical and non-medical factors that are not specified in the ambulance guidelines and that appear to contribute to the decision.

Conclusion

In OHCA patients transported with ongoing CPR the survival rate significantly declines when time on scene increases. Patients transported within 20 minutes of time on scene have the highest survival rate, this suggests the decision to transport with ongoing CPR needs to be made early in the resuscitation process.

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Conflict of interest statement

Author CG received a speaker's fee from Stryker. RWK is the recipient of the funding for maintaining the ARREST database.

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CHAPTER 7

Time to Return of Spontaneous Circulation and Survival: When to Transport in out-of-Hospital Cardiac Arrest?

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Prehospital Emergency Care. 2020; 7: 1-11

Abstract

Background
In out-of-hospital cardiac arrest (OHCA), 10-50% of patients have return of spontaneous circulation (ROSC) before hospital arrival. It is important to investigate the relation between time-to-ROSC and survival to determine the optimal timing of transport to the hospital in patients without ROSC.

Methods
We analyzed data of OHCA patients with a presumed cardiac cause (excluding traumatic and other obvious non-cardiac causes) and ROSC before hospital arrival from the Amsterdam Resuscitation Study (ARREST) database. ROSC included those patients whose ROSC was persistent or transient before or during transport, lasting ≥1 minute. Of these data, we analyzed the association between the time of emergency medical services (EMS) arrival until ROSC (time-to-ROSC) and 30-day survival.

Results
Of 3632 OHCA patients with attempted resuscitation, 810 patients with prehospital ROSC were included. Of these, 332 (41%) survived 30 days. Survivors had a significant shorter time-to-ROSC compared to non-survivors of median 5 min (IQR 2,10) vs. median 12 min (IQR 9,17) ($p<0.001$). Of the survivors, 90% achieved ROSC within 15 minutes compared to 22 minutes of non-survivors. In a multivariable model adjusted for known system determinants time-to-ROSC per minute was significantly associated with 30-day survival (OR 0.89; 95%CI 0.86 – 0.91). A ROC curve showed 8 minutes as the time-to-ROSC with the best test performance (sensitivity of 0.72 and specificity of 0.77).

Conclusion
In OHCA patients with prehospital ROSC survival significantly decreases with increasing time-to-ROSC. Of all patients, 90% of survivors had achieved ROSC within the first 15 minutes of EMS resuscitation. The optimal time for the decision to transport is between 8 and 15 minutes after EMS arrival.

Introduction

During out-of-hospital-cardiac-arrest (OHCA), in the Netherlands, emergency medical services (EMS) deliver advanced life support (ALS) on scene. The resuscitation on scene ends when a patient is either transported to the hospital emergency department (ED) with or without return of spontaneous circulation (ROSC) or when the resuscitation is terminated on scene.[1] In general, in only 10% to 50% of patients, ALS results in ROSC on scene.[2-5] Previous studies have investigated the relationship between duration of cardiopulmonary resuscitation (CPR) until ROSC and outcome. Longer CPR duration was associated with worse (neurologic) outcome after OHCA.[4-10]

Both the European Resuscitation Council (ERC) guidelines and the American Heart Association (AHA) guidelines generally accept withdrawing of further resuscitation in case of asystole for more than 20 minutes during ALS on scene. [1,11,12] However, the Guidelines do not describe the optimal time on scene until a decision to transport without ROSC should be made. At the start of resuscitation, it is not known if a patient will achieve ROSC and when, but there is evidence that there is an association between time of on-scene resuscitation and 30-day survival of patients transported without ROSC.[13] Waiting until the decisional moment at 20 minutes of ALS could, therefore, impair the chance of survival of those who should be transported without ROSC.

Transportation without ROSC may impair the quality of CPR but is potentially beneficial if treatment options can be applied that are generally unavailable in the pre-hospital setting. Extracorporeal cardiopulmonary resuscitation (ECPR) is such a treatment, although the precise indications and its limitations are not yet well defined in the context of OHCA.[14-16] For this reason, the optimal duration of resuscitation on scene and when transport should be initiated in patients without ROSC is important but rarely studied.[17] Therefore, this study aims to determine the rate and time of prehospital ROSC and 30-day survival and investigate the optimal timing of the decision to initiate transport without ROSC.

Methods

Study setting and design

This study used data from the Amsterdam Resuscitation Study (ARREST). ARREST is an ongoing prospective registry of all-cause OHCA in North-Holland, a province of the Netherlands. The study region covers an area of 2404 km^2 and had a population of 2.8 million in 2015. The present study covered the study period between January 1, 2014, to December 31, 2016. All patients with a presumed cardiac cause of the OHCA (excluding traumatic and other obvious non-cardiac causes) and documented prehospital ROSC were included. Exclusion criteria were: patients who live outside the Netherlands, ROSC after Automated External Defibrillator (AED) defibrillation before EMS arrival and EMS witnessed arrests. The medical ethics review board of the Amsterdam UMC, Academic Medical Center (AMC), approved the study including the use of data of deceased patients. From all surviving patients, we obtained deferred consent.

EMS system in the study region

In case of a medical emergency, the national emergency number will be dialed and if the dispatcher suspects an OHCA, two EMS teams are dispatched. Each team consists of a driver, who is qualified to perform BLS, and a paramedic, who is qualified to perform ALS. Simultaneously with EMS, first responders are dispatched, equipped with an AED. These first responders are firefighters and police officers trained in BLS and AED use. Dispatchers also alert citizen-responders who use AEDs placed in public areas in the study region. Anyone in the study region is allowed to use these AEDs. The EMS follow a national protocol for cardiac arrest based on the European guidelines.[1] According to the national protocol, if a patient does not achieve ROSC despite ALS, EMS can consider termination of resuscitation in case of any non-shockable rhythm for 20 minutes. Considering transport is recommended in patients with shockable rhythm or treatable cause, but the optimal time on scene that transport without ROSC should be initiated is not specified. The EMS paramedics are qualified and legally allowed to make termination of resuscitation decisions in the prehospital setting without consulting a physician. There were no hospitals in the region that used ECPR as a treatment strategy in OHCA patients during the current study period.

Data collection

In the ARREST study, data are registered using the Utstein templates for resuscitation registries, this is described elsewhere.[18,19] After a resuscitation, EMS routinely sends the continuous electrocardiogram (ECG) from their manual defibrillator and an EMS run report to the ARREST study center. If an AED was connected, ARREST study personnel visited the AED site shortly after the OHCA to collect the AED ECG recording. We analyzed the ECGs from the EMS manual defibrillator and AEDs with dedicated software. For each recording, we corrected clock drift of EMS defibrillators and AEDs to standardized times. From these ECG recordings, we determined the first monitored rhythm, time of the first defibrillation and time of the moment of ROSC.

Time intervals and definitions

We collected time-stamped data on the emergency call at the dispatch center, EMS arrival on scene, first defibrillation and moment of ROSC. We defined the time of EMS arrival on scene as the moment the EMS manual defibrillator was connected to the patient. The moment of ROSC we defined as the time of first recognizable cardiac rhythm compatible with cardiac output, in absence of chest-compressions on the ECG lasting at least 1 minute, analyzed using CODE-STAT software (Stryker Emergency Care, Redmond, WA. USA). In addition to cardiac rhythm, we used a sustained increase in $EtCO_2$ and/or undulations in the electrodes impedance signal synchronous with QRS complexes, in the absence of chest compressions, to define the time of ROSC (eFigure 1).

ROSC could be intermittent or transient before or during transport. We defined 'time to ROSC' as the interval between EMS arrival and ROSC. Two independent assessors (CG & DD) determined the moment of ROSC in 100 cases. To assess the consistency of measurement made by multiple observers measuring the same quantity of the continuous variable 'time to ROSC', we used the intraclass correlation coefficient (ICC).[20,21] For a subgroup analysis of potential ECPR patients we selected patients with: age between 18-75 years, a shockable initial rhythm and a witnessed arrest as criteria.

Outcome

The primary outcome of this study was overall 30-day survival, based on information from the National Civil Registry. As secondary outcome, we used the Cerebral Performance Category (CPC 1-5) at hospital discharge to assess the neurological and functional outcome (CPC 1= good cerebral performance, CPC 2 = moderate cerebral disability, CPC 3 = severe cerebral disability, CPC 4 = persistent vegetative state, and CPC 5 = brain death or clinical death).[22] We defined a good neurologic outcome as CPC 1 or CPC 2.

Statistical analysis

We present categorical variables as percentages and continuous variables as mean and standard deviation (SD) or as median and interquartile range (IQR) depending on the data distributions. To compare categorical data we used chi-square statistics. For continuous data, we used unpaired t-test, Jonckheere-Terpstra test or Mann-Whitney U test when appropriate. We used the log-rank test to compare Kaplan Meier graphs of the cumulative proportion of ROSC over time. To display the ability of achieving ROSC (as a positive test) to predict survival as a function of increasing time of resuscitation (per 1 minute time junctures) before ROSC, we constructed a receiver operating characteristic (ROC) curve with the corresponding area under the curve (AUC). To calculate the sensitivity (Sn) we used as the true positive rate the cumulative proportion of those achieving ROSC at increasing time of resuscitation and who did survive at least 30 days. To calculate the specificity (Sp) we used as the true negative rate the remaining proportion of those who did not have achieved ROSC yet at increasing time of resuscitation and who did not survive at least 30 days. We used Youden's J statistic ($J = Sn + Sp - 1$) to determine the time juncture in the resuscitation that yielded the best test performance.[23] To investigate the independent association between time to ROSC and 30-day survival we used a multivariable logistic regression model. In the model, all variables significantly associated in univariate analysis were included. In the model, the number of events per variable was 10.[24] We performed a subgroup analysis of potential ECPR patients and their association between time to ROSC and 30-day survival. We reported the odds ratio with 95% confidence intervals (CI) and associated p values. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics 24 (IBM Corporation, Armonk, NY).

Results

Of 8023 patients with suspected OHCA in the study period, 3632 had attempted resuscitation by EMS. Of these, 1008 patients did achieve prehospital ROSC of which 810 patients were included for analysis (Figure 1). In 21 (3%) patients ROSC was achieved after transport was already initiated. The clinical baseline characteristics of the 121 patients with missing ECG data were not significantly different from those that were included for analysis (eTable 1). Of the 810 patients with ROSC, 342 (42%) were considered potential ECPR patients, based on our selection criteria.

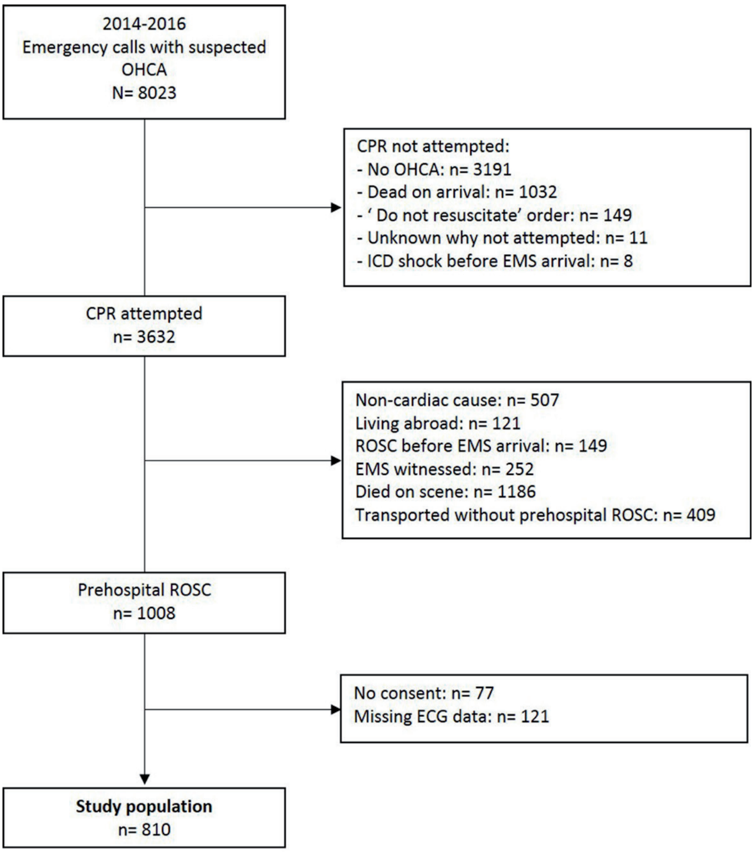


Figure 1. Flow chart of patient inclusion 2014-2016

Patients, process and time to ROSC characteristics

Table 1 shows the characteristics of patients who achieved ROSC and the subgroup of potential ECPR patients. The moment of ROSC was determined with an intraclass correlation coefficient of 0.987 (95% CI 0.981-0.991), indicating an excellent level of reliability. The median time to ROSC in all patients was 9 (IQR 5, 15) minutes and 7 (IQR 3, 13) in potential ECPR patients. Table 2 shows the differences between patients when time to ROSC was divided into time interval categories. Patients who achieved ROSC earlier were significantly younger, had a higher proportion of a shockable first monitored rhythm, had their arrest more often in a public location, had more often a bystander witnessed arrest and had more often bystander CPR (all p-values <0.001). Patients with a short time to ROSC interval had a higher proportion of AED connection and AED defibrillation. Figure 2 shows the cumulative proportion of ROSC for patients with no defibrillation, first shock by an AED and first shock by EMS. Patients who received the first shock by an AED had significantly earlier ROSC compared to patients with the first shock by EMS and patients with no defibrillation (log-rank p-value <0.001).

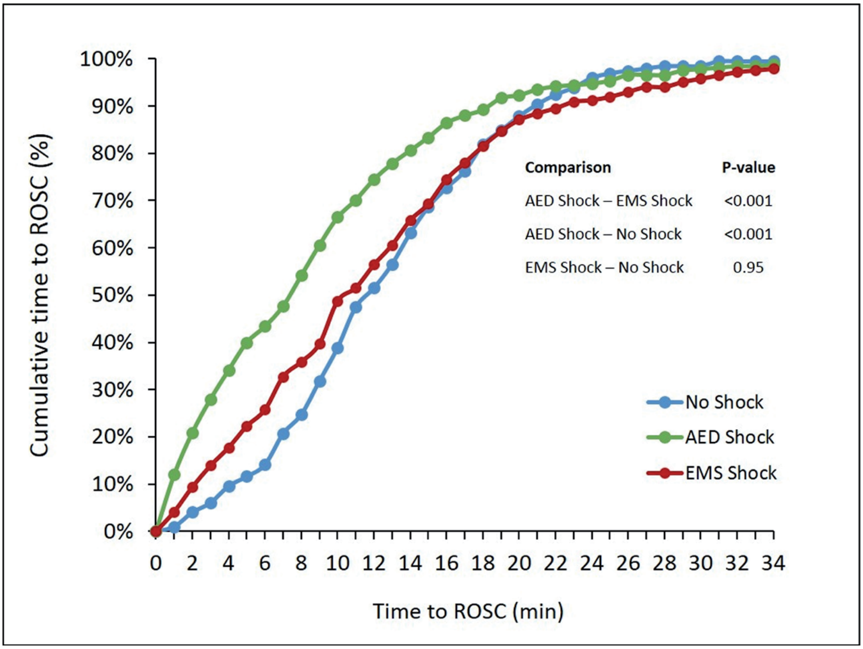


Figure 2. Time to ROSC and defibrillation. Cumulative proportion of ROSC (%) over time (min) in patients with a first shock by AED (n=325), first shock by EMS (n=287) and no shock (n=198) compared with the log-rank test.

Table 1: Characteristics, outcome of all patients with prehospital ROSC and potential ECPR patients

	All patients with ROSC N=810	Potential ECPR patients N=342
Pre-OHCA factors		
Age, years, mean (SD)	67 (14)	60 (10)
Sex, n (%)		
Male	590 (73%)	286 (84%)
Female	220 (27%)	56 (16%)
Resuscitation parameters		
First monitored rhythm, n (%)		
Shockable (VF/VT)	519 (66%)	342 (100%)
Not shockable	268 (34%)	-
Location of arrest, n (%)		
Residential	540 (67%)	190 (56%)
Public	268 (33%)	151 (44%)
Witnessed arrest, n (%)		
Not witnessed	160 (20%)	-
Bystander witnessed	642 (80)	342 (100%)
CPR before EMS arrival, n (%)		
No Bystander CPR	131 (16%)	45 (13%)
Bystander CPR	675 (84%)	297 (87%)
AED connected, n (%)	475 (59%)	201 (59%)
AED shock delivered, n (%)	325 (40%)	196 (57%)
Time intervals		
Call to EMS arrival, minutes, median (IQR 25,75)	11 (9,13)	10 (8,13)
Call to first defibrillation, minutes, median (IQR 25,75)*	8 (6,10)	8 (6,10)
EMS arrival to ROSC, median (IQR 25,75)	9 (5,15)	7 (3,13)
Outcome		
ROSC before transport	789 (97%)	332 (97%)
Admitted to hospital from ED, n (%)	623 (81%)	322 (95%)
30-day survival, n (%)	332 (41%)	237 (70%)
Good neurologic outcome, CPC 1-2, n (%)‡	272 (35%)	204 (63%)

ROSC- return of spontaneous circulation; CPR - cardiopulmonary resuscitation; VF/VT - ventricular fibrillation/tachycardia; EMS - emergency medical services; ED – emergency department; SD - standard deviation; IQR - inter-quartile range.
* if shockable rhythm, both AED and mDFB defibrillation ‡ CPC score at hospital discharge
Percentages shown are column percentages

Table 2: Time to ROSC intervals and outcome of patients with prehospital ROSC

	Time to ROSC <5 min N=216	Time to ROSC ≥5 - 10 min N=216	Time to ROSC ≥10 - 15 min N=172	Time to ROSC ≥15 min N=206	P for trend	Missing N (%)
Pre-OHCA factors						
Age, years, mean (SD)	65 (14)	68 (15)	68 (15)	69 (13)	<0.002	-
Sex, n (%)					0.24	-
Male	166 (77%)	156 (72%)	119 (69%)	150 (73%)		
Female	50 (23%)	60 (28%)	53 (31%)	56 (27%)		
Resuscitation parameters						
First monitored rhythm, n (%)					<0.001	23 (3%)
Shockable (VF/VT)	181 (86%)	143 (68%)	91 (56%)	104 (51%)		
Not shockable	29 (14%)	67 (32%)	73 (44%)	99 (49%)		
Location of arrest, n (%)					<0.001	2 (<1%)
Residential	114 (53%)	149 (69%)	119 (70%)	158 (77%)		
Public	102 (47%)	67 (31%)	51 (30%)	48 (23%)		
Witnessed arrest, n (%)					<0.001	8 (1%)
Not witnessed	16 (7%)	50 (23%)	37 (22%)	58 (29%)		
Bystander witnessed	200 (93%)	164 (77%)	134 (78%)	144 (71%)		
CPR before EMS arrival, n (%)					<0.001	4 (<1%)
No Bystander CPR	18 (8%)	27 (13%)	31 (18%)	55 (27%)		
Bystander CPR	198 (92%)	189 (87%)	141 (82%)	147 (73%)		
AED connected, n (%)	151 (70%)	134 (62%)	94 (55%)	96 (47%)	<0.001	-
AED shock delivered, n (%)	130 (60%)	86 (40%)	55 (32%)	54 (26%)	<0.001	-

	Time to ROSC <5 min N=216	Time to ROSC ≥5 - 10 min N=216	Time to ROSC ≥10 - 15 min N=172	Time to ROSC ≥15 min N=206	P for trend	Missing N (%)
Time intervals						
Call to EMS arrival, minutes, median (IQR 25,75)	11 (8,13)	11 (9,13)	11 (9,13)	11 (9,14)	0.16	-
Call to first defibrillation, minutes, median (IQR 25,75)*	7 (6,9)	8 (7,11)	8 (7,11)	9 (7,11)	0.22	2 (<1%)
EMS arrival to ROSC, median (IQR 25,75)	2 (1,4)	8 (6,9)	12 (11,14)	19 (17,24)	<0.001	-
Outcome						
ROSC before transport	216 (100%)	215 (99%)	172 (100%)	186 (90%)	<0.001	-
Admitted to hospital from ED, n (%)	195 (92%)	175 (85%)	131 (78%)	122 (65%)	<0.001	37 (5%)
30-day survival, n (%)	162 (75%)	94 (44%)	46 (27%)	30 (15%)	<0.001	-
Good neurologic outcome, CPC 1-2, n (%)†	141 (68%)	77 (37%)	33 (20%)	21 (10%)	<0.001	23 (3%)

ROSC- return of spontaneous circulation; CPR - cardiopulmonary resuscitation; VF/VT - ventricular fibrillation/tachycardia; EMS - emergency medical services; ED – emergency department; SD - standard deviation; IQR - inter-quartile range. * if shockable rhythm, both AED and mDFB defibrillation † CPC score at hospital discharge

Percentages shown are column percentages

Outcome

Of the 810 patients with ROSC before hospital arrival, 187 (19%) died in the emergency room, 623 (81%) were admitted to the hospital and 332 (41%) survived at least 30 days. Of patients who survived at least 30 days, 272 of 332 patients (88%) had a good neurologic outcome. Survivors who achieved ROSC earlier had a higher proportion of good neurologic outcome. (p<0.001). Differences in the survival of patients with prehospital ROSC are shown in eTable 2. In the subgroup of potential ECPR patients, 237 (70%) patients survived at least 30 days with 204 (86%) of these having a good neurologic outcome.

Time to ROSC and 30-day survival

Figure 3A shows the cumulative proportion of ROSC over time in survivors and patients who died. Time to ROSC was significantly shorter in survivors compared to non-survivors with a median of 5 min (IQR 2, 10) compared to 12 min (IQR 9, 17), respectively (p<0.001). The cumulative proportion of ROSC over time of survivors was significantly earlier than patients who died (log-rank p-value p<0.001). The probability of outcome and time to ROSC is shown in Figure 3B. In patients who achieve ROSC within 15 minutes the probability to survive at least 30 days is greater than the probability to die, after 15 minutes to ROSC the probability is reversed. The sensitivity and specificity of time to ROSC and 30-day survival are displayed in a ROC curve with an AUC of 0.77 (Figure 4). This ROC curve shows 8 minutes as the best test performance time point with the highest sensitivity (0.66) and specificity (0.77).

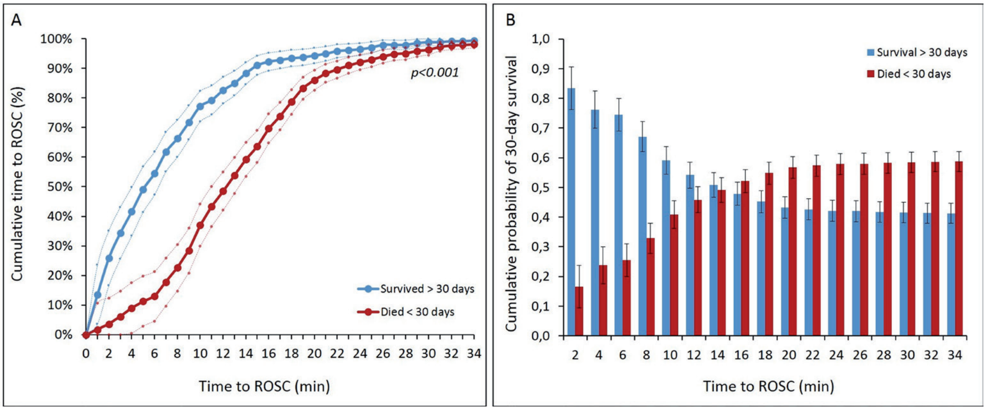
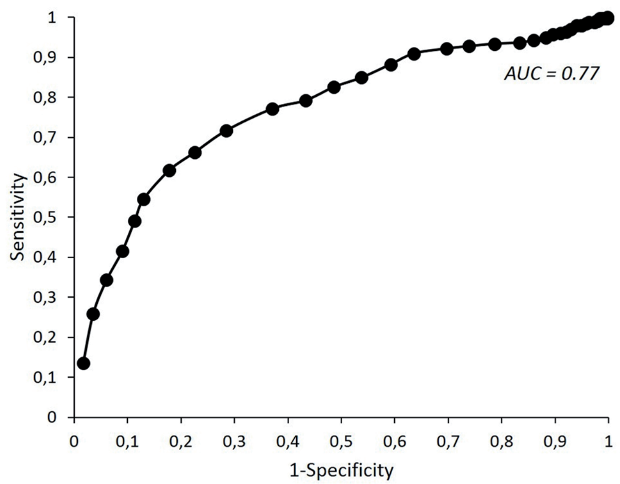


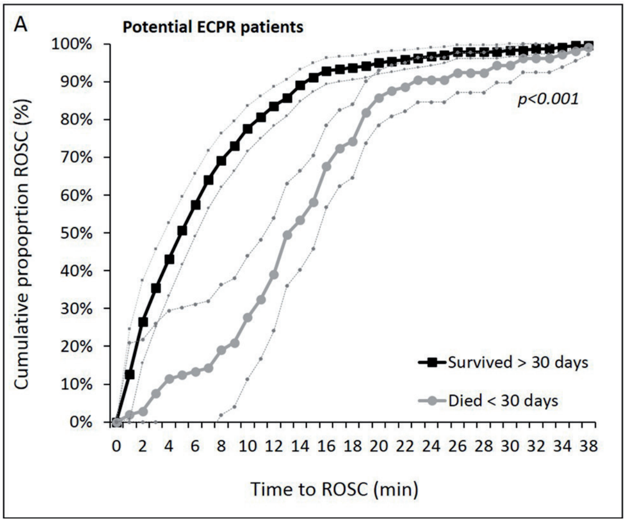
Figure 3. Time to ROSC and 30-day survival. Fig 3A: Cumulative proportion of ROSC (%) over time (min) in patients with 30-day survival (n=332) and patients who died (n=478) compared with the log-rank test. **Fig 3B:** Probability of outcome (30-day survival or death) over time (min). (For example: of the patients who had ROSC within 10 minutes (cumulative proportion of 433 patients), 256 patients survived and 177 died, making the probability to survive 0.59 (256/433) and the probability to die 0.41 (177/433)).

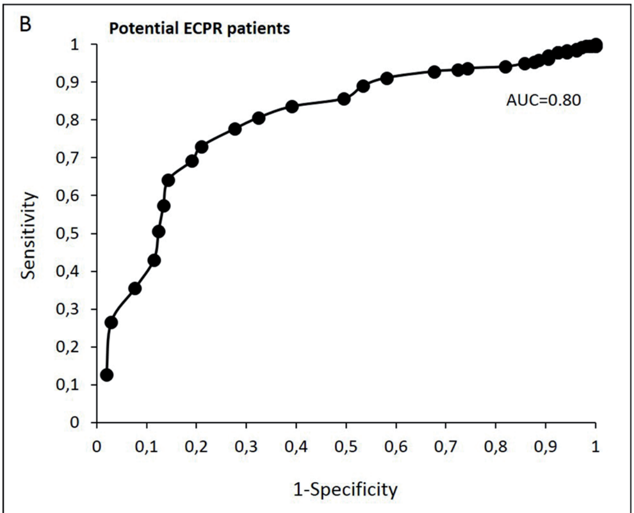


Min	2	4	6	8	10	12	14	16	18	20	22	>22
Sn	0.26	0.42	0.55	0.66	0.77	0.83	0.88	0.92	0.93	0.94	0.96	>0.96
Sp	0.96	0.91	0.87	0.77	0.63	0.51	0.41	0.30	0.21	0.14	0.10	<0.10

Figure 4. ROC curve time to ROSC. ROC curve with achieving ROSC (as a positive test) to predict survival as a function of increasing time of resuscitation (per 1 minute time junctures) before ROSC. (For example: at the time juncture of 8 minutes 220 of the total of 332 survivors achieved ROSC, making the sensitivity 0.66 (220/332) and 370 of the total of 478 patients who died, did not yet have achieved ROSC, making the specificity 0.77 (370/478)).

In the subgroup of potential ECPR patients also the time to ROSC was significantly shorter in survivors compared to non-survivors with a median of 5 min (IQR 2,9) compared to 13 min (IQR 9,18), respectively ($p<0.001$). Also, the cumulative proportion of ROSC over time of survivors was significantly earlier than patients who died in the ECPR potential subgroup (figure 5A). The ROC curve of potential ECPR patients (figure 5B) shows 9 minutes as the best test performance time point (sensitivity 0.73 and specificity 0.79) in this subgroup.





Min	2	4	6	8	10	12	14	16	18	20	22	>22
Sn	0.27	0.43	0.57	0.69	0.78	0.84	0.89	0.93	0.94	0.95	0.96	>0.96
Sp	0.97	0.89	0.88	0.81	0.72	0.61	0.47	0.32	0.26	0.14	0.11	<0.10

Figure 5. Time to ROSC and 30-day survival in the subgroup of potential ECPR patients. Fig 5A: Cumulative proportion of ROSC (%) over time (min) in potential ECPR patients with 30-day survival (n=237) and patients who died (n=105) compared with the log-rank test. **Fig 5B:** ROC curve of potential ECPR patients with achieving ROSC (as a positive test) to predict survival as a function of increasing time of resuscitation (per 1 minute time junctures) before ROSC.

In a multivariable model that included all significant factors for survival, time to ROSC was independently associated with 30-day survival in both all patients (OR 0.89; 95% CI 0.86 – 0.91) and the subgroup of potential ECPR patients (OR 0.88; 95% CI 0.85 – 0.91); for every minute the duration of the resuscitation increased before ROSC, the odds of 30-day survival decreased (Table 3). To exclude an effect of transport on time to ROSC and survival, the model was also calculated excluding the 21 patients in which ROSC was achieved after transport was already initiated. In this model time to ROSC was also independently associated with 30-day survival (OR 0.87; 95% CI 0.84 – 0.90).

Table 3a. Multivariable logistic regression of variables associated with 30-day survival of all patients

	Unadjusted		Adjusted	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Time to ROSC, per min	0.87 (0.85 – 0.89)	<0.001	0.89 (0.86 – 0.91)	<0.001
Age, per year	0.95 (0.94 – 0.96)	<0.001	0.95 (0.94 – 0.97)	<0.001
Male gender	2.57 (1.82 – 3.63)	<0.001	1.19 (0.71 – 1.99)	0.51
Public location	3.10 (2.29 – 4.19)	<0.001	1.62 (1.07 – 2.45)	0.02
Bystander witnessed	4.19 (2.71 – 6.48)	<0.001	1.98 (1.11 – 3.52)	0.02
Bystander CPR	1.66 (1.12 – 2.48)	0.013	0.65 (0.36 – 1.17)	0.15
Response time	0.91 (0.87 – 0.95)	0.001	0.93 (0.88 – 0.98)	0.004
Initial shockable rhythm	44.05 (22.15 – 87.60)	<0.001	29.33 (13.84 – 62.16)	<0.001

Table 3b. Multivariable logistic regression of variables associated with 30-day survival of potential ECPR patients

	Unadjusted		Adjusted	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Time to ROSC, per min	0.88 (0.85 – 0.91)	<0.001	0.88 (0.85 – 0.91)	<0.001
Age, per year	0.95 (0.93 – 0.98)	<0.001	0.96 (0.93 – 0.99)	0.003
Male gender	0.95 (0.53 – 1.83)	0.95	N/A	
Public location	1.89 (1.17 – 3.05)	0.009	1.64 (0.96 – 2.81)	0.07
Bystander CPR	1.44 (0.75 – 2.77)	0.27	N/A	
Response time, per min	0.96 (0.90 – 1.01)	0.13	N/A	

OR - odds ratio; CI - confidence interval; ROSC - return of spontaneous circulation; CPR - cardiopulmonary resuscitation

Discussion

Our study showed that in OHCA patients with prehospital ROSC the survival rate significantly declined when the duration of resuscitation to ROSC increased. Time to ROSC was independently associated with 30-day survival. When considering both the benefit of achieving ROSC on scene and the benefit of early transport if ROSC cannot be achieved, our time to ROSC analyses indicated that the best time for the decision to transport appears to be between 8 and 15 minutes after EMS arrival, if ROSC is not yet achieved and 9 minutes for potential ECPR patients. Nevertheless, it is uncertain if transporting these patients within the suggested time window will increase survival rates.

Of all patients who survived up to 30 days, 90% had achieved ROSC within the first 15 minutes. This is earlier than previous studies which found that in patients with 30-day survival (and good neurologic outcome) 90% achieved ROSC within 16 to 24 minutes.[4-7,10,17,25] The difference in outcome between our study and previous studies can be explained by choice of the study population, (for example, selecting only patients with a witnessed arrest[4,8]) and differences in prehospital resuscitation characteristics (for example AED use before EMS arrival).

In our study, 59% of patients who achieved prehospital ROSC had an AED connected and 40% of all patients had an AED shock delivered before the arrival of the EMS. This is a high number compared to other studies with typical AED defibrillation rates of 3-15%.[4,8-10] Recently Zijlstra et al. found that OHCA patients surviving 30 days or more, are increasingly defibrillated by AEDs before EMS arrival.[26] Patients who received the first shock by an AED had significantly shorter time to first defibrillation and earlier ROSC compared to patients with a first shock by EMS. However, there was no significant difference in survival between patients who received the first shock from an AED or EMS.

Our study showed that characteristics that are known to be associated with 30-day survival (age, public location, bystander witnessed, response time and first shockable rhythm) also were associated with shorter time to ROSC. Nevertheless, the multivariable model showed that time to ROSC was independently and inversely associated with 30-day survival and the incremented value of waiting for ROSC on scene diminishes. At the same time delay to transport without ROSC is associated with lower 30-day survival.[8,13,17] ERC and AHA guidelines do not describe a specific moment for a decision to transport if ROSC is not (yet) achieved on scene. According to the ERC, the decision to transport with ongoing CPR should be weighed after 10 minutes of passed on-scene resuscitation, but this time point is not supported with data.[12] ERC and AHA guidelines generally accept withdrawing further resuscitation, in case of asystole for more than 20 minutes during ALS on scene. Only the duration of resuscitation on scene as a criterion for termination of resuscitation is not enough.[11,12] Our study showed that already after 15 minutes the odds of achieving ROSC and survive as well, are less than 10%. The decision to transport for all patients that may meet certain criteria must clearly be made well before termination is even considered.

Previously published data from the ARREST registry shows that in the Netherlands this is generally not the case. [13] In patients without ROSC who were transported with ongoing CPR the median time on scene was 25 (IQR 19, 32) minutes before the start of transport. In patients without ROSC who were not transported, the median time on scene before termination of resuscitation was 23 (IQR 17, 28) minutes.

When resuscitation efforts on scene fail there is a need for a treatment strategy in the hospital that cannot be done in the prehospital setting. The treatment strategy has to be beneficial enough for patients without ROSC to exceed the "cost" of transport (diminished quality of CPR during transport and safety of crew).[27] Although randomized studies are lacking, ECPR is a treatment strategy that could benefit a selected group of OHCA patients, in which conventional resuscitation efforts do not result in ROSC.[15] Grunau et al. suggests 16 minutes of on-scene resuscitation as the optimal moment to transport balancing the risks between early transport with ongoing CPR and the possibility of achieving ROSC on scene.[17] Our study shows that overall, after 15 minutes the probability of 30-day survival is lower than the probability to die within 30 days. In our study, 8 minutes was the time point with the highest combined sensitivity and specificity, in the potential ECPR patients subgroup this time point was 9 minutes. An approach that considers the total utility of earlier vs. later transport could be more useful.[28] However, in our study it was not possible to assign weights to sensitivity and specificity, neither can we assign cost utilities to earlier transport. Furthermore, although we performed a potential ECPR patients subgroup analysis, with (generally common) criteria: age between 18-75 year, shockable initial rhythm and witnessed arrest, the precise indications and limitations of ECPR are not yet well defined in the context of OHCA.[14,15] Therefore, taken into account the overall ROC optimal time point and the point where the probability of 30-day survival is smaller than the probability to die, 8 to 15 minutes of on-scene resuscitation would be a good time interval to start transport to the hospital for ECPR if conventional resuscitation efforts do not result in ROSC.

ECPR requires fully trained staff that are readily available upon the decision to transport the patient to the hospital. Local practices still vary widely but immediate decision making upon arrival in patients without ROSC is paramount and should incorporate these described intervals for best outcomes.[15] Patients without ROSC almost always achieve normal heart rhythm after ECPR initiation but neurological outcome so far remains unpredictable.[14]

Limitations

Several issues need to be considered in the interpretation of our findings. In this study, we only present results from the group of patients who achieved pre-hospital ROSC. However, we documented earlier the rapidly worsening survival when transport without ROSC is delayed.[13] Our recommendation combined information from both studies.

Only a small proportion of our patient population achieved ROSC after transport was initiated. We do not know if, in patients who were transported without ROSC, the chances of achieving ROSC were different than if in the same patients the resuscitation was continued on scene. This question can only be studied when an early or later moment of transport without ROSC is determined at random. To our knowledge, such a study has never been performed. Finally, due to the observational character of this prospective cohort, only an independent association and not causality between the moment of ROSC and survival could be determined.

Future research

Only randomized trials on early vs. later transport without ROSC can yield information that elucidates the optimal time for a decision to transport and if transport is beneficial for those in refractory arrest. Randomized studies are also necessary to research ECPR as a beneficial treatment for patients who do not respond to conventional resuscitation efforts and define for which patients and when.

Conclusion

In OHCA patients with prehospital ROSC, survival significantly decreases with increasing time to ROSC. Of all patients, 90% of survivors had achieved ROSC within the first 15 minutes of EMS resuscitation and statistically, 8 minutes was the time point with the highest combined sensitivity and specificity for transport. We suggest that the optimal time for the decision to transport is between 8 and 15 minutes after EMS arrival.

Funding

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Conflict of interest statement

CG received a speaker's fee from Stryker. RWK is the recipient of the funding for maintaining the ARREST database.

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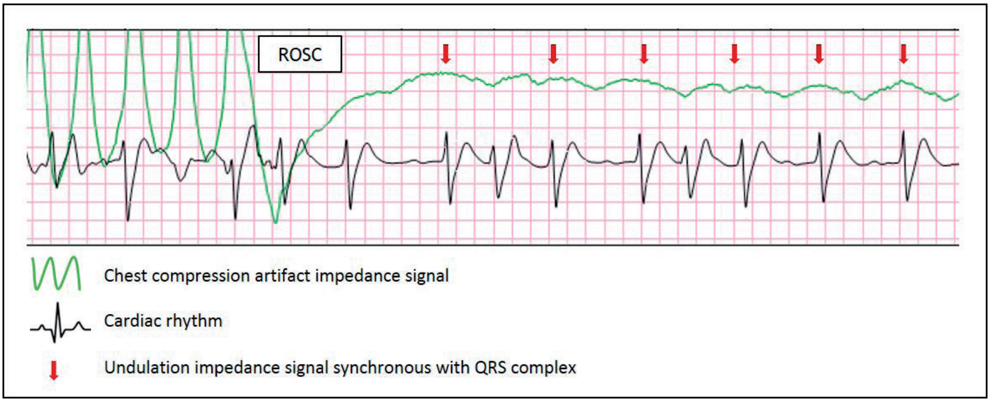
Supplementary materials



eFigure 1. Determing ROSC on ECG

eTable 1. Characteristics of OHCA patients with missing ECG data

	Study population N=810	Missing N=121	P-value	Missing
Pre-OHCA factors				
Age, years, mean (SD)	67 (14)	65 (15)	0.2	-
Sex, n (%)			0.8	-
Male	590 (73%)	87 (72%)		
Female	220 (27%)	87 (72%)		
Resuscitation parameters				
First monitored rhythm, n (%)			0.4	69 (7%)
Shockable (VF/VT)	519 (66%)	53 (71%)		
Not shockable	268 (34%)	22 (29%)		
Location of arrest, n (%)			0.01	2 (<1%)
Residential	540 (67%)	66 (55%)		
Public	268 (33%)	55 (45%)		
Witnessed arrest, n (%)			0.4	13 (1%)
Not witnessed	160 (20%)	27 (23%)		
Bystander witnessed	642 (80%)	89 (77%)		
CPR before EMS arrival, n (%)			0.1	8 (<1%)
No Bystander CPR	131 (16%)	26 (22%)		
Bystander CPR	675 (84%)	91 (78%)		
AED used	475 (59%)	63 (52%)	0.2	-
Outcome				
30-day survival, n (%)	332 (41%)	49 (41%)	0.9	-

CPR - cardiopulmonary resuscitation; VF/VT - ventricular fibrillation/tachycardia; EMS - emergency medical services;.
Percentages shown are column percentages

7

eTable 2. Characteristics of OHCA patients with prehospital ROSC survivors vs non-survivors

	Non survivors N=478	Survivors N=332	p-value	Missing N (%)
Pre-OHCA factors				
Age, years, mean (SD)	71 (13)	62 (14)	<0.001	-
Sex, n (%)			<0.001	-
Male	314 (66%)	276 (83%)		
Female	164 (34%)	58 (17%)		
Resuscitation parameters				
First monitored rhythm, n (%)			<0.001	23 (3%)
Shockable (VF/VT)	204 (44%)	315 (97%)		
First Shock AED*	121 (59%)	182 (58%)		
First Shock EMS*	83 (41%)	133 (42%)		
Not shockable	259 (56%)	9 (3%)		
Location of arrest, n (%)			<0.001	2 (<1%)
Residential	367 (77%)	173 (52%)		
Public	109 (23%)	159 (48%)		
Witnessed arrest, n (%)			<0.001	8 (1%)
Not witnessed	132 (28%)	28 (8%)		
Bystander witnessed	340 (72%)	302 (92%)		
CPR before EMS arrival, n (%)			0.012	4 (<1%)
No Bystander CPR	90 (19%)	41 (12%)		
Bystander CPR	384 (81%)	291 (88%)		
Time intervals				
Response time, minutes, median (IQR 25,75)	11 (9,14)	10 (8,13)	<0.001	-
Call to first defibrillation, minutes, median (IQR 25,75)†	9 (7,11)	8 (6,10)	<0.001	2 (<1%)
Time to ROSC, median (IQR 25,75, 90, 99)	12 (9,17, 22, 42)	5 (2,10, 15, 33)	<0.001	-
Outcome				
ROSC before transport	463 (97%)	326 (98%)	0.24	-
Admitted to hospital from ED, n (%)	291 (66%)	332 (100%)	<0.001	37 (5%)

ROSC- return of spontaneous circulation; CPR - cardiopulmonary resuscitation; VF/VT - ventricular fibrillation/tachycardia; EMS - emergency medical services; ; ED – emergency department; SD - standard deviation; IQR - inter-quartile range.
* calculated proportion of shockable rhythm first shocked by AED or EMS
† in patients with shockable rhythm, both AED and mDFB defibrillation
Percentages shown are column percentages

CHAPTER 8

8

To transport or to terminate resuscitation on-site. What factors influence EMS decisions in patients without ROSC? A mixed-methods study

C. de Graaf, A.T.C.M. de Kruif, S.G. Beesems, R.W. Koster

Resuscitation. 2021; 164: 84-92

Abstract

Background

If a patient in out-of-hospital cardiac arrest (OHCA) does not achieve return of spontaneous circulation (ROSC) despite advanced life support, emergency medical services can decide to either transport the patient with ongoing CPR or terminate resuscitation on scene.

Purpose

To determine differences between patients without ROSC to be transported vs. terminated on scene and explore medical and nonmedical factors that contribute to the decision-making of paramedics on scene.

Methods

Mixed-methods approach combining quantitative and qualitative data. Quantitative data on all-cause OHCA patients without ROSC on scene, between January 1, 2012, and December 31, 2016, in the Amsterdam Resuscitation Study database, were analyzed to find factors associated with decision to transport. Qualitative data was collected by performing 16 semi-structured interviews with paramedics from the study region, transcribed and coded to identify themes regarding OHCA decision-making on the scene.

Results

In the quantitative Utstein dataset, of 5870 OHCA patients, 3190 (54%) patients did not achieve ROSC on scene. In a multivariable model, age (OR 0.98), public location (OR 2.70), bystander witnessed (OR 1.65), EMS witnessed (OR 9.03), and first rhythm VF/VT (OR 11.22) or PEA (OR 2.34), were independently associated with transport with ongoing CPR. The proportion of variance explained by the model was only 0.36. With the qualitative method, four main themes were identified: patient-related factors, local circumstances, paramedic-related factors, and the structure of the organization.

Conclusion

In patients without ROSC on scene, besides known resuscitation characteristics, the decision to transport a patient is largely determined by non-protocolized factors.

Introduction

During an out-of-hospital-cardiac-arrest (OHCA), emergency medical services (EMS) deliver advanced life support (ALS) on scene. When a patient does not achieve return of spontaneous circulation (ROSC) despite ALS, EMS can decide to either transport the patient with ongoing CPR or terminate the resuscitation on scene.[1] In general, 50-90% of OHCA patients do not achieve ROSC on scene.[2-5] The European Resuscitation Council (ERC) guidelines recommend termination of resuscitation (TOR) in case of asystole for more than 20 minutes during ALS and recommend that transport with ongoing CPR should be considered in case of EMS witnessed arrest, ROSC at any moment, a shockable initial rhythm or a presumed reversible cause.[1,6] There is evidence that delaying a decision to transportation until termination rules can be applied will impair the chance of survival of those who should be transported without ROSC.[7] Previous research has shown that the decision to start transport with ongoing CPR could be influenced by factors such as compromised scene safety, the expectation of the public, and environmental circumstances.[8-11]

In the Netherlands, paramedics are legally allowed to make TOR decisions in the pre-hospital setting without consulting a physician. It is rarely documented which factors contribute to the decision to transport or terminate resuscitation of a patient when resuscitation appears to be unsuccessful. This study aims to explore medical and nonmedical factors that determine the decision to transport or terminate resuscitation on scene and to determine the differences between patients without ROSC that are transported or resuscitation terminated on scene.

Methods

Design

We designed a sequential mixed-methods approach to quantitatively assess the data of OHCA patients without ROSC on scene and to qualitatively assess the perception of paramedics on factors contributing to the decision to transport these patients. The purpose of pairing qualitative and quantitative components within this study was to provide a better understanding of these paramedic's decisions.[12]

Quantitative Method

Study setting and patient population

For the quantitative part of this study we used the data from the Amsterdam Resuscitation Study (ARREST). The ARREST study is an ongoing prospective registry of all-cause OHCA in the Northwest part of the Netherlands. We included all-cause OHCA patients without ROSC on scene with attempted resuscitation between January 1, 2012 and December 31, 2016. Exclusion criteria were (transient) ROSC before transport and unknown ROSC status before transport. The medical ethics review board of the Amsterdam UMC, Academic Medical Center (AMC), approved the study including the use of data of deceased patients. Deferred consent was obtained from all surviving patients. In the Netherlands there is no donation procedure in case of out-of-hospital cardiac arrest, therefore patients are not transported with ongoing CPR for the purpose of organ donation. The specifics on the EMS system in the region and the ARREST data collection are described elsewhere.[7,13,14]

Time intervals and definitions

Time-stamped data on the emergency call at the dispatch center, EMS arrival on scene, EMS departure from scene, and arrival at the emergency department (ED) were collected to create time intervals. EMS arrival on scene was defined as the moment the EMS manual defibrillator was connected to the patient. The 'time to decision' of EMS was the interval between EMS arrival on scene and departure of the ambulance from the scene. In cases of EMS witnessed arrests, 'time to decision' was the interval between the collapse and departure of the ambulance from the scene. If the resuscitation was terminated on scene, 'time to decision' was the interval between EMS arrival and disconnection of the EMS manual defibrillator at the moment of termination. Information regarding (transient) ROSC was obtained from the EMS report.

Outcome

The outcome of this study in the quantitative analysis was transport with ongoing CPR to the hospital or TOR.

Statistical analysis

Categorical variables were presented as percentages and continuous variables as mean and standard deviation (SD) or as median and interquartile range (IQR) depending on the data distribution. To investigate independent associations between resuscitation variables and transport we used a multivariable logistic regression model. In the model, all variables significantly associated with univariate analysis were included. We used the Hosmer-Lemeshow test for the goodness of fit and the Nagelkerke test to assess the explained variance of the model. We reported the odds ratio with 95% confidence intervals (CI) and associated p-values. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics 26 (IBM Corporation, Armonk, NY).

Qualitative method

Semi-structured interviews were used to explore unknown (non)medical factors that may contribute to the decision to start transport or terminate the resuscitation on scene.

Sample

Paramedics from the four regions in the study area were invited to participate in the study. Selection criteria were: at least 1 year of work experience as an EMS paramedic and participating in at least 10 OHCAs. Interested paramedics were informed about the purpose of the study and when they agreed to participate, informed consent was obtained.

Interviews

For the semi-structured in-depth interviews a topic-list was developed based on the results of the quantitative part of this study and previous research (Supplemental data 1a, eTable 1).[8-11] Topics were about the decision-making on scene and factors contributing to the decision to transport or terminate the resuscitation on scene. We used a narrative approach to encourage the paramedics to share their experiences on scene during resuscitation. Each interview lasted 30-45 min. An in-depth interview is a conversation with a specific research purpose, and the focus lies on the informant's perception of self, life, and experience, expressed in his or her own words. This allows the researcher to understand the personal interpretations of social reality that individuals hold.[15] All interviews were conducted by CG at the location of the participant's choice (either at home or the EMS station). To ensure validity and reduce possible bias every participant received a summary of the interview to check for accuracy of interpretation.

Analyses

All tape-recorded interviews were transcribed verbatim using a thematic content analysis based on comparisons within and across respondents.[16] Data analysis of the first four interviews were done by two researchers (AdK and CG) so that they could agree upon a method of coding. The remaining analyses were performed by CG. Details of the analysis of the interviews are described in Supplemental data 1b

Results

Quantitative results

In 5870 of 12348 patients with suspected OHCA resuscitation was started by EMS. Of these, 3190 (54%) patients did not achieve ROSC on scene. Of these, resuscitation was terminated on scene in 2269 patients and 921 patients were transported with ongoing CPR (Figure 1).

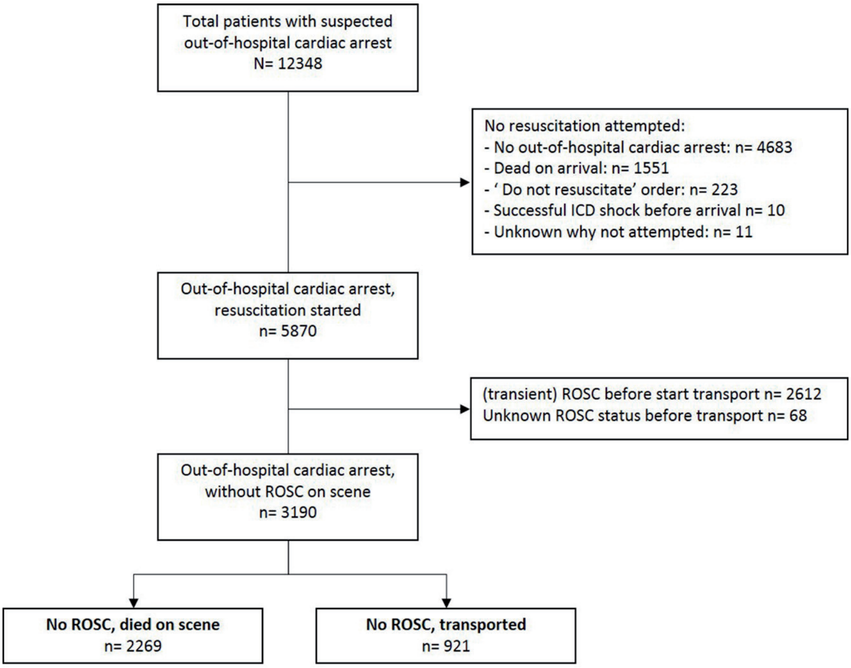


Figure 1: Flowchart of patient inclusion.

Baseline patient and process characteristics

Patient and process characteristics of patients without ROSC on scene are shown in Table 1. In a multivariable model, age, public location, bystander witnessed arrest, EMS witnessed arrest, and first rhythm VF/VT or PEA, were independently associated with transport with ongoing CPR. (Table 2) The variance explained by the model was 0.36.

Table 1. Baseline characteristics of OHCA patients who died on scene and patients transported with ongoing CPR

	No ROSC and died on scene N=2269	No ROSC and transported N=921	P-value	Missing N (%)
Pre-OHCA factors				
Age, years, mean (SD)	67 (16)	63 (15)	<0.001	57 (2%)
Sex, n (%)			<0.001	2 (0.1%)
Female	735 (33%)	188 (21%)		
Male	1515 (67%)	695 (79%)		
Resuscitation parameters				
First monitored rhythm, n (%)*			<0.001	252 (8%)
VF/VT	270 (13%)	417 (52%)		
PEA	685 (33%)	256 (32%)		
Asystole	1127 (54%)	128 (16%)		
Presumed cause, n (%)			0.38	1 (0.1%)
Medical	2046 (91%)	810 (92%)		
Not medical	206 (9%)	72 (8%)		
Location of arrest, n (%)			<0.001	1 (0.1%)
Residential	1856 (83%)	518 (59%)		
Public	395 (17%)	365 (41%)		
Witnessed arrest, n (%)			<0.001	37 (1.2%)
Not witnessed	1041 (47%)	185 (21%)		
EMS witnessed	76 (3%)	108 (12%)		
Bystander witnessed	1108 (50%)	580 (33%)		

	No ROSC and died on scene N=2269	No ROSC and transported N=921	P-value	Missing N (%)
CPR before EMS, n (%) **			0.41	30 (1%)
No Bystander CPR	383 (18%)	147 (19%)		
Bystander CPR	1742 (82%)	612 (81%)		
AED connected, n (%)**			0.07	1 (0.1%)
No	810 (38%)	316 (41%)		
Yes	1339 (62%)	448 (59%)		
First defibrillation by ***			0.34	1 (0.1%)
AED	227 (48%)	270 (51%)		
EMS manual defibrillator	249 (52%)	257 (49%)		
Time intervals				
Response time, minutes, median (IQR 25,75)	12.3 (9.8, 15.3)	11.5 (9.4, 14.6)	0.001	509 (16%)
Call to first defibrillation, minutes, median (IQR 25,75)***	9.6 (7.5, 11.5)	9.3 (7.1, 12.0)	0.40	1 (0.1%)
Time to decision, minutes, median (IQR 25,75)	22.8 (17.3, 27.9)	24.9 (18.8, 30.7)	<0.001	649 (20%)

Chi-square statistics were used to compare categorical data. For continuous data unpaired t-test or Mann-Whitney U test was used when appropriate.
CPR- cardiopulmonary resuscitation; VF/VT - ventricular fibrillation/tachycardia; PEA - pulseless electrical activity; EMS - emergency medical services; SD - standard deviation; IQR - inter-quartile range; ED – emergency department.
* in case of EMS witnessed, first monitored rhythm is rhythm at collapse; ** if not EMS witnessed; *** if shockable first rhythm (including AED shocks)
Percentages shown are column percentages

Table 2. Multivariable logistic regression of variables associated with transport

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Age, per year	0.98 (0.98 – 0.99)	0.98 (0.97 – 0.99)
Male	1.79 (1.49 – 2.16)	1.16 (0.91 – 1.48)
Public location	3.31 (2.79 – 3.93)	2.70 (2.13 – 3.41)
Bystander witnessed*	2.95 (2.45 – 3.55)	1.65 (1.29 – 2.11)
EMS witnessed*	8.00 (5.73 – 11.15)	9.03 (5.89 – 13.85)
First rhythm**		
VF/VT	13.60 (10.71 – 17.26)	11.22 (8.45 – 14.89)
PEA	3.29 (2.61 – 4.15)	2.34 (1.75 – 3.11)
Respons time, per minute	0.99 (0.98 -1.01)	-

Hosmer and Lemeshow Test P: 0.114
Nagelkerke R Square: 0.36
OR - odds ratio; CI - confidence interval; EMS - emergency medical services; VF/VT - ventricular fibrillation/tachycardia; PEA - pulseless electrical activity;
* reference category: not witnessed
**reference category: asystole

Qualitative results

Sixteen paramedics from four different EMS regions each, were interviewed (Table 3). Figure 2 displays the identified four main themes and corresponding subthemes. For each main theme representative quotes illustrating different subthemes are shown in table 4. Additional illustrating quotes for each subtheme are shown in Supplemental data 1c, eTable 2.

Table 3. Characteristics of the 16 paramedics interviewed

	Paramedic Interviews N=16
Age, years, median (IQR 25,75)	49 (41, 52)
Sex, n (%)	
Male	10 (63%)
Female	6 (37%)
EMS work experience, years, median (IQR 25,75)	18 (13, 22)
Attempted OHCA's, n, median (IQR 25,75)	100 (93, 200)

EMS - emergency medical services; OHCA - Out-of-hospital cardiac arrest;
SD - standard deviation; IQR - inter-quartile range
*The age and gender distribution of the paramedics interviewed are representative of the work force in this region. According to Dutch EMS statistics, 70% of all paramedics is between 35-54 years old, with a gender distribution of 65% male and 35% female paramedics.

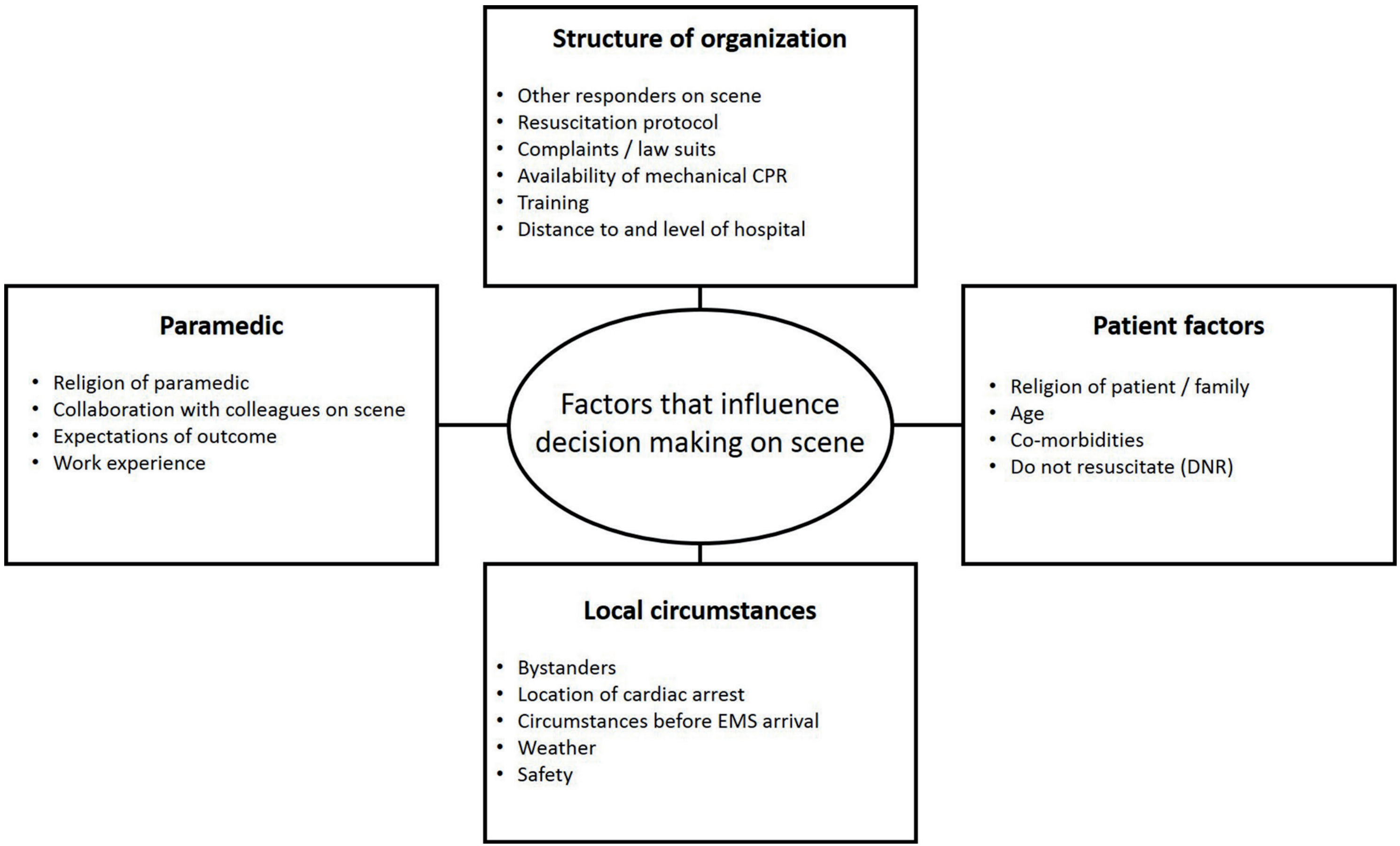


Figure 2: Summary figure qualitative data. Main themes and subthemes identified after analysis and coding of the qualitative data.

Table 4. Illustrative quotations for contributing themes in the decision-making process on scene

Theme	Subtheme	Illustrative quotes
Patient related factors	Religion	"I told the wife of a patient: 'we really do not have anything more we can do, this is the end'. The response was: 'I want you to try it, only then it is god's will' I said: 'Well, if you think that's the only way, we will go on.'" (Paramedic A, male, 59 yr, 20 years of work experience) "
	Co-morbidities	"Advanced cancer without viable treatment options or end stage cancer, dementia, old age with extensive heart failure or extensive COPD. […] you should be more withholding with resuscitation, or at least the survival chances for these patients are very small. I will not immediately transport these patients."(Paramedic E, male, 40yr, 14 years of work experience)
Local Circumstances	Bystanders	"In particular, family from time to time can be very pressing and insisting. Especially, when you are only with two or four, you are quickly outnumbered and the only thing you can say is: 'When the situation asks for it we will transport to the hospital but keep in mind that the hospital will do very little more.' The only advantage at that moment is that the decision will be taken in a more quiet environment" (Paramedic H, male, 54yr, 16 years of work experience)
	Circumstances before EMS arrival	"Sometimes you cannot know how long someone is down and when the collapse occurred and you have to start anyway. However, if I know for sure that someone is down for a long time or that it is actually futile to resuscitate, than I will stop." (Paramedic I, female, 48yr, 20 years of work experience)
	Weather	"If you are resuscitating on the streets in a heavy rain shower, well than you say: 'let's go into the car'. […] 'he is now in the car, so just continue and drive to the hospital'." (Paramedic K, male, 45yr, 18 years of work experience)
	Safety	"Well, then a firearm was shown and we were told: 'You will go for transport, right?' Of course sir..' " (Paramedic H, male, 54yr, 16 years of work experience)
Paramedic	Collaboration on scene	"[…] it is unspoken rule that if someone objects to stop, than we will transport. Because in the end you want that, that someone has a comfortable feeling or the feeling that he has done everything he could and does not arrive at home with a guilt feelings. " (Paramedic E, male, 40yr, 14 years of work experience)
	Expectations on outcome	"[…] we resuscitated continuously for a long time on a very bad patient and who in the end did make it to the hospital. […] the neurological damage was way less than we had expected. That really surprised me. So maybe we need more of those success stories so we think like maybe we should lower the threshold to transport." (Paramedic E, male, 40yr, 14 years of work experience)
	Work experience	" At the start of my career, it was difficult for me to take a decision about someone's life. I am in service now for 21 years and have seen so much, it is easier to take it." (Paramedic F, female, 49yr, 21 years of work experience)

Theme	Subtheme	Illustrative quotes
Structure of organization	Protocol	"I think, which protocol you have to follow also influences your motivation very much. But I think that if you go in the direction of the asystole/PEA protocol you unknowingly are less motivated to go on,[…]."(Paramedic K, male, 45yr, 18 years of work experience)
	Mechanical CPR	"[…], the moment mechanical CPR was introduced the number of people who were transported with asystole increased. […], patients just went underneath the device and got transported because the device was on. However when you stop that device you just see asystole and you have to ask yourself if you want to continue or not." (Paramedic G, male, 49yr, 22 years of work experience, worked in both EMS regions with and without mechanical CPR)
	Training	"The training on resuscitation skills is very good, however there is less training on what other considerations you can take into account and how you can play a role in what you can do justice to the patient and family. Because you can do justice to the family if you do everything you can, but also when you do nothing." (Paramedic A, male, 59 yr, 20 years of work experience) "

CPR- cardiopulmonary resuscitation; VF/VT - ventricular fibrillation/tachycardia; PEA - pulseless electrical activity; EMS - emergency medical services

Patient-related factors

Religion of the patient and family, age of the patient, comorbidity, and the Do Not Resuscitate (DNR) status could influence the decision-making on scene. The family may pressure paramedics, because according to their religion everything has to be done including transport for further care. The age of the patient, in particular very young patients, influences paramedics to transport a patient, regardless of the result of the resuscitation effort. Conversely, advanced age could be a factor for some paramedics to withhold the decision to transport:

"For me, I think the age of a patient plays a role, I do have some reservations to resuscitate people who are very old, even if they are vital. They do not get any better from it. "(Paramedic C, male, 42yr, 7 years of work experience)

In patients with severe comorbidities such as end-stage cancer, dementia, and extensive heart-or pulmonary disease paramedics are more reluctant in the decision to transport. In case of disagreement between family members regarding the DNR status of the patient, the resuscitation was continued or even transport to the hospital could be chosen to escape from the situation.

Local circumstances

Bystanders presence, the OHCA location, circumstances before EMS arrival, weather conditions, and safety could influence the decision-making. Paramedics reported that they decided to transport when bystanders, especially family, insisted and exerted pressure to transport or continue CPR. It was often mentioned that the hospital was a safer place or a quieter environment, which would make it easier for the family to accept termination of resuscitation. Also, in a public location (e.g. streets, church) paramedics would favour transport to remove the patient from the situation. Circumstances as witnessed OHCA, AED use, and BLS before EMS arrival, influence the opinion on the chances of the patient and therefore also the decision to transport a patient. Weather conditions (e.g. heavy rain or cold) led to the decision to treat the patient in the ambulance and when a patient was already in the ambulance, the decision to transport was made faster. Transport was also accelerated by unsafe local circumstances such as the location itself (e.g. freeway) or by threats from bystanders or family.

Paramedic-related factors

The religion of the paramedic, collaboration with colleagues, expectations of the outcome, and work experience, could influence decision-making. Some paramedics reported that the religion of a colleague influenced a decision and those colleagues often continued the resuscitation when others would have stopped:

"I did have one colleague who was very religious, he wanted to resuscitate everyone even if someone was totally asystolic." (Paramedic G, male, 49yr, 22 years of work experience)

In the collaboration on scene, when conflicting opinions between team members occurred, the opinion to transport generally prevailed over the opinion to terminate on scene. The expectation of the outcome influenced the decision, positive experiences with patients who survived despite a bad situation on scene led to more transport decisions. Paramedics reported that during the early years of their careers, the decision to stop was more difficult to make and they transported more often instead of terminating the resuscitation on scene. Years of experience made the decision to stop on scene easier.

Structure of the organization

Non-medical responders on scene, resuscitation protocol, complaints or lawsuits, availability of mechanical CPR, training, and available hospitals could influence the decision-making on scene. The non-medical responders on scene (police and firefighters) sometimes wondered why CPR was stopped but this did not influence the decision to stop or transport. In general, the resuscitation protocol is clear regarding the termination of resuscitation, illustrated by the fact that in the case of patients in PEA or asystole paramedics report to agree on termination. The experience of complaints or lawsuits could influence the decision to transport patients:

"Actually, just as with every complaint, incident, or possible suboptimal functioning, people will get more careful, they feel hurt and will transport and present patients more easily. That way they will step by step build a new level of confidence until something happens again." (Paramedic H, male, 54yr, 16 years of work experience)

Paramedics reported that with the introduction of mechanical CPR it was easier to transport patients to the hospital with ongoing CPR and paramedics from regions without the availability of mechanical CPR reported they would probably transport more patients if they had mechanical CPR. They also indicate that there could be more focus on communication and social skills when deciding to terminate resuscitation in training according to paramedics. In general, the level of the hospital or distance to the hospital did not influence the decision. Sometimes if the distance to a hospital was relatively long, a physician was contacted for consultation before the decision to transport or termination was made.

Discussion

Our study showed that the factors in quantitative data that were associated with transport only explained 36% of the variance in the decision to transport without ROSC. There was a number of cases where the reason for the decision to transport or to terminate resuscitation was not clear from the quantitative data, indicating that additional factors contributed to that decision. Clearly, our quantitative factors did not describe the process of the decision to transportation sufficiently. The additional variance could be explained by findings of our qualitative research: factors related to the patient, to local circumstances, to the paramedic himself, and to the structure of organization were identified as important additional themes contributing to the decision to transport a patient with ongoing CPR.

A recent review identified similar themes and classified as: the arrest event, patient characteristics, the resuscitation scene, resuscitation provider perspective and medico legal concerns.[17] The review indicated that the resuscitation provider perspective is missing from resuscitation decision-making literature. Our study provides insights on the provider perspective and is an extension of pre-existing literature. A qualitative study using vignettes and focus groups, identified six domains of influencing factors in EMS provider decision-making.[18] Factual information, structural, cultural, interpersonal, safety risk and personal were the domains identified, factors within these domains were similar to the themes in our study (e.g. personal safety, experience of paramedic, age of the patient and the view of colleagues).

According to ERC guidelines, transportation with ongoing CPR should be considered in case of an EMS witnessed arrest, ROSC at any moment, a shockable initial rhythm or a presumed reversible cause, and the guidelines recommend to withdraw further resuscitation in case of asystole for more than 20 minutes during ALS.[1,6] In our study both quantitative and qualitative data show that an EMS witnessed arrest and a shockable initial rhythm indeed contribute to the decision to transport and asystole as rhythm to the decision to terminate the resuscitation. Factors such as BLS and AED use before EMS arrival were mentioned in the qualitative study to contribute to the decision to transport but this was not shown in the quantitative data.

Factors within four main themes could be identified: patient-related factors, local circumstances, paramedic-related factors, and the structure of the organization. Patients transported with ongoing CPR was significantly younger than patients where the resuscitation was terminated. This quantitative finding was complemented in the interviews: paramedics experienced the resuscitation of patients of older age as futile, and even if such a patient survived, the likelihood of a good neurologic outcome was considered questionable. Also, co-morbidities such as end-stage cancer, dementia, and extensive heart or pulmonary disease were factors in which paramedics were more reluctant to decide to transport. Obviously such beliefs can create a self-fulfilling prophecy. We know from previous research that resuscitation-related factors and not comorbidity determine outcome after OHCA in elderly patients and that the resuscitation of older patients is not useless because the vast majority of survivors have a favorable neurologic outcome.[19] This indicates that sometimes paramedics now make decisions based on outdated information.

Local circumstances influenced the decision in multiple ways. An OHCA at a public location more often is being witnessed, receives bystander CPR, has an AED attached, and has a shockable initial rhythm. These are all resuscitation characteristics that positively influence the outcome.[13,20,21] We found that an OHCA in a public location encourages transport independently of these factors, indicating there is more to the decision in public than only resuscitation-based characteristics. If a scene was unsafe because of its location (f.e. highway) or because of pressure or threats from bystanders the decision was made to transport a patient with ongoing CPR to a safer place. This finding is supported by previous literature which also found that scene safety influenced EMS practice.[8]

Several paramedic-related factors were identified with the qualitative part of this mixed-methods study. Experience strengthens confidence and decision-making of paramedics.[22,23] In our study, clinical experience influenced on-site decision-making, particularly the decision to stop and end the resuscitation on scene was reported as being easier to make through the years of experience. Consequently, this means less experienced paramedics will probably transport more OHCA patients to the hospital because of uncertainty. However, it is not certain if the decision made by the most experienced, indeed is the best decision.

Within the structure of the organization, the availability of mechanical CPR was reported to influence the decision to transport. Manual CPR in a moving ambulance reduces the quality of CPR and potentially harms the paramedic.[24,25] Mechanical CPR can ensure the quality of CPR and safety of the paramedics during transport.[24,26] The consequence mentioned in the interviews is that paramedics tend to transport patients with mechanical CPR who would otherwise be left at the scene. This may result in the transport of patients with a very poor prognosis and more pressure on hospital resources.

Another factor within the organizational theme was resuscitation training. Paramedics reported that they experience that in training and post-arrest evaluation the emphasis is on resuscitation skills resulting in a successful resuscitation, while they should welcome more attention to end-of-life decision-making and improving communication skills with bystanders or family. Teaching and discussing Termination of Resuscitation issues as described in our study could be included in training scenarios. Literature suggests that regular training and education help paramedics making the right decisions, while the ability of sharing experiences after an cardiac arrest, for example through a debriefing with feedback, helps to cope with decision-making on scene.[27,28]

Limitations

One of the limitations that has to be taken into account is that the use of interested paramedics as participants for the semi-structured interviews could create a selection bias. Except possibly having relatively longer work experience, the characteristics of the paramedics that we interviewed (Table 3) does not suggest bias in age and sex of the paramedics. In view of the exploratory nature of the qualitative part of this study we were still able to gain insight in the decision-making on scene. Another limitation is that the qualitative data collected by the interviews do not provide information on how often in daily practice such a factor will contribute to the decision.

Future research

Future studies will be necessary to verify our findings, quantify how much the identified factors contribute to the decision and study whether it is possible to influence these factors in the decision-making process in daily practice.

Conclusion

In patients without ROSC on scene known resuscitation characteristics only explain part of the variance in the decision to transport. Additional factors contribute to the decision-making on scene such as age and comorbidities of the patient, pressure by family or bystanders, the safety of the OHCA location, work experience of the paramedic, the experience of an incident or lawsuit, and the availability of mechanical CPR.

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Conflict of interest statement

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Supplementary materials

Supplemental data 1a

eTable 1: Topic guide and examples of questions semi structured interviews

General characteristics interviewee	
	Age
	Gender
	Education to become an EMS Paramedic
	Years of work experience as an EMS Paramedic
	Work region
	Estimate of treated OHCA cases
Opening question	
	How do you make the decision to either terminate a resuscitation on scene or transport a patient without ROSC?
Patient factors	
	What kind of patient characteristics influence your decision, and in which way?
	What kind of co-morbidities are important and do you take into account when making the decision?
	In what way does the age of the patient contribute in your decisions?
Resuscitation characteristics	
	What kind of factors do you take into account that happened before your arrival? (for example, delay, start of basic life support, witnessed status, placement of automated external defibrillator)
	What kind of influence has the notification the EMS dispatch center gives you on your decision?
Experience	
	Do you feel like you have the competence and skills to make the decision to either terminate of transport a patient with ongoing CPR?
	When you look back at all your cardiac arrest cases and experiences, would you have changed anything?
Guidelines	
	Can you tell me if there were situations during your career where the guidelines and protocols did not help you in the decision to either transport or terminate?
Personality / Attitude	
	Do you want to be resuscitated yourself?
	Which cardiac arrest case made the greatest impression on you?
	What is your opinion on the guidelines and protocols regarding resuscitation?
	What is your expectation of the outcome of transport with ongoing CPR after a cardiac arrest?
Colleagues and collaboration	
	Do you think there is a difference in decision making between male of female colleagues?
	Has there ever been a situation where you did not agree with the decision of a colleague? What happened during that situation?
	When working together with colleagues, who takes the responsibility of the decision to terminate or transport?
Complaints, prosecution and disciplinary cases?	
	Has there ever been a case of complaint, prosecution or disciplinary case on the decision making during resuscitation? Did that influence the decision making afterwards?
Religion	
	What is the influence of your own religion on the decision making during a resuscitation?
	What is the influence of the religion of the patient (and family) on the decision making during a resuscitation?
	What is the influence of the religion of colleagues on the decision making during a resuscitation?

Location of patient (home / public)	
	In what way does the location of the patient influences your decision to terminate or transport the patient?
	Is there a difference in decision making for a patient resuscitated in public compared to a resuscitation in a home setting?
	Does the location of the patient in home (for example in high or small building) influence the decision making?
Environment	
	Did you ever encounter a situation where you were forced to make another decision than what you wanted due to circumstances? What were those circumstances?
	In what way do people (spectators or family) who a present, influence the decision making?
	How do you communicate the decision with family of the patient and did you ever encounter any problems?
Safety	
	Did you ever feel threatened during a resuscitation and in what way did that influence your decision making?
	What is your opinion on the safety of transport with ongoing CPR?
Weather conditions	
	What kind of weather conditions influence the decision making to transport or terminate the resuscitation?
Other responders (police and firefighters)	
	What is the influence of police and fire fighters in the decision making?
Mobile medical team (MMT) with physician on board (in case of traumatic or pediatric arrest)	
	What is your experience with the MMT and the decision to terminate or transport a patient with ongoing CPR?
	Has there ever been a situation where you did not agree with the decision of the MMT? What happened during that situation?
Mechanical chestcompression devices	
	Does your EMS region have mechanical CPR?
	Did the introduction of mechanical CPR change your decision to transport or terminate? In what way?
Hospital	
	In what way does the distance to the hospital influence your decision to transport or terminate?
	What are your expectations when you arrive at the hospital with ongoing CPR?
Closing question	
	Do you have any additional factors or topics you would like to addres regarding the decision making during a resuscitation?

Supplemental data 1b

Interview analysis

First, the transcripts were read multiple times and divided into segments of text, and codes (labels) were assigned to these segments (open coding). Subsequently, codes were grouped into categories and these categories were used to create themes. Next, the categories of the several transcripts were related to one another (axial coding). The codes were all organized into a mind map, using dedicated software (FreeMind, GNU General Public License, version 1.00). Finally a selection of the different themes which illustrated the contributing factors in the decision-making by paramedics on scene and fit into the broader overall 'story' that the data told us, to investigate differences and similarities between the findings from the quantitative and qualitative analyses. All findings were discussed in the whole research team twice, once in a preliminary stage to discuss the codes and themes, and once to discuss the interrelations between the themes and quantitative analyses to reach the main findings.

Supplemental data 1c

eTable 2. Additional illustrative quotations for contributing themes in the decision-making process on scene

Theme	Subtheme	Illustrative quotes
Patient related factors	Age	"When you are talking about adults, you will just treat them according to protocol and at that moment I will treat someone of 25 years the same as someone of 80 years" (Paramedic B, male, 44yr, 18 years of work experience) "For me I think the age of a patient plays a role, I do have some reservations to resuscitate people who are very old, even if they are vital. They do not get any better from it. "(Paramedic C, male, 42yr, 7 years of work experience) "Children I will always resuscitate and also go on transport with ongoing CPR to the hospital. Actually that is kind of an agreement within our EMS and also in the aftercare for parents, they seem to be dealing with it better if in the end everything what is possible has been done for the child."(Paramedic D, male, 55yr, 22 years of work experience)
	Do Not Resuscitate (DNR)	"Well, if they say we have a DNR order and it comes from all angles and from reliable sources. Yes, than we are allowed to just stop. Not if someone simply just shouts it, only if the general practitioner can confirm it, than we will stop." (Paramedic F, female, 49yr, 21 years of work experience) "Once I experienced, that at a certain moment the family became ad odds with each other. Two daughters said that their father did not want all of this, at that moment another person entered the room and said, that their father did want to be resuscitated. So an argument within the family arose, well between family. At that moment I thought: 'it is so unclear if there is a DNR order or not stating what the father would have wanted, we will just start with the resuscitation and we will go to the hospital.'" (Paramedic G, male, 49yr, 22 years of work experience)
Local Circumstances	Location of OHCA	"Sometimes in public spot, that is where you sometimes decide to transport also earlier or at least you go for transport. There are two things that can happen then. Either you go on transport very quickly, within the protocol and then you arrive within the protocol at the emergency department. Or we quickly go into the ambulance and proceed with the resuscitation there and bring them to the mortuary. Those are the options in which you think, ok, at least than someone is not in the church, the middle of the street or sidewalk anymore." (Paramedic E, male, 40yr, 14 years of work experience)

Theme	Subtheme	Illustrative quotes
	Circumstances before EMS arrival	"Yes, if an AED has defibrillated and BLS has been adequately performed, than a patient just has more chance." (Paramedic J, female,36yr, 6 years of work experience) "The people of course with witnessed arrest, well with those I will always continue." (Paramedic G, male, 49yr, 22 years of work experience) "For a couple of times, they did not know what was going on and we also had no idea what was going on, so we did decide to transport."(Paramedic E, male, 40yr, 14 years of work experience)
	Weather	"You can imagine that you will quickly be hypothermic outside, so if it is very cold and snowing and someone lies down on the streets, you will pick him up quickly and go into the ambulance. We have learned that you have to prevent at all times the death of someone in your ambulance. Because you will get trouble with a death person in your car which will be declared as a non-natural cause of death. If you choose to go into the ambulance than you will also transport." (Paramedic C, male, 42yr, 7 years of work experience)
	Safety	"Look, it is fine beside a freeway, because you can just close it. Although that will not really guarantee the safety. So in general if it is possible and you have the space than you will leave, just because it is not safe." (Paramedic A, male, 59 yr, 20 years of work experience)
Paramedic	Religion	"I did have one colleague who was very religious, he wanted to resuscitate everyone even if someone was totally asystolic." (Paramedic G, male, 49yr, 22 years of work experience) "Not in resuscitation practice, we all had the same training and do all work according to the same protocol. Religion has nothing to do with it." ."(Paramedic D, male, 55yr, 22 years of work experience)
	Collaboration on scene	"However, it is so, as the second ambulance, I do give my opinion and I will engage that discussion shortly on scene because you do not have the time for it. If there is no consensus, then I will focus on the decision of the first ambulance."(Paramedic L, male, 51yr, 9 years of work experience)
	Expectations on outcome	"If you would ask me now how often I have seen that people retrieve rhythm and output after they arrived at the hospital. I don't dare to answer, but I cannot name five who had VF during transport and walked out of the hospital. So the survivors are people who retrieve rhythm and output at home or on the street and the remainder are a sad category." (Paramedic M, male, 52yr, 26 years of work experience)
Structure of organisation	Other responders on scene	"I have been bothered by this now and then, when we decided to terminate a resuscitation also if this was not a traumatic one. At that moment, mainly fire fighters could sometimes act unpleasant. I would say: 'guys, excuse me but this is futile'. I must say that for the past couple of years I did not experienced this anymore. However in the early days, this may resulted into dispute." (Paramedic M, male, 52yr, 26 years of work experience)

Theme	Subtheme	Illustrative quotes
	Resuscitation Protocol	"Do not follow protocols blindly, but also use arguments, that is how it should be. It cannot be that you say, well this is an old person so I stop. It can be an argument, however you have to think what is your action and why do you act like that." (Paramedic L, male, 51yr, 9 years of work experience) "Firstly, you have the protocol which you have to follow. People with persistent VF, those you have to try to transport as soon as possible."(Paramedic C, male, 42yr, 7 years of work experience) "We once had a girl of 17 years old, where we called for hyperventilation. I connect her to the monitor and saw a complete heart block. I thought, how is this possible in a child of 17, I did not even though that and she turns asystole. At that moment everybody thinks, what happens here?! Although we have an asystole protocol, we are going to take here with us." (Paramedic F, female, 49yr, 21 years of work experience)
	Complaints or Law suits	"Look, you must not continue resuscitating because you are afraid of problems. If you just properly follow the protocol and have proper arguments, there is nothing to worry about." (Paramedic I, female, 48yr, 20 years of work experience) "Actually just as with every complaint, incident, or possible suboptimal functioning, people will get more careful, they feel hurt and will transport and present patients more easily. That way they will step by step build a new level of confidence until something happens again." (Paramedic H, male, 54yr, 16 years of work experience)
	Availability of mechanical CPR	"Maybe, with mechanical CPR you even will go on transport with asystole or anything in case of a younger person instead of the situation now where we cannot go anywhere, so we complete the protocol at home. With mechanical CPR you could say, we round it up, put everything in the car and go. Because we can ventilate and give medication on the way, we do not have to stay at home for this. I think maybe the only difference is that we will transport more people who will now eventually be left at home according to protocol." (Paramedic F, female, 49yr, 21 years of work experience, EMS region without mechanical CPR)
	Available Hospitals	"If you have to travel for another half hour, than you will contact the cardiologist that you still have to travel for half an hour. So at that moment you will consulate with a cardiologist." " (Paramedic N, female, 51 yr, 22 years of work experience) " "No, if you decide to transport than the distance must not matter. "(Paramedic L, male, 51yr, 9 years of work experience)

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PART 4

Summary, discussion and future perspectives

New technologies and decision making in out-of-hospital cardiac arrest

Summary

In this thesis, we performed analyses on basic life support and AED use by first responders and advanced life support by EMS. We evaluated the impact of AED use, assessed the clinical benefit of new AED technology, and gained more insight into patients transported without ROSC and the decision-making of the EMS on scene.

Part 1: Occurrence of shockable initial rhythm

Chapter 2

In chapter 2 we studied the proportion of shockable initial rhythm and whether it is still declining over a 10-year time period, across multiple emergency medical services (EMS) in four different European countries (Denmark, Norway, Sweden, Netherlands). Furthermore, we studied if there was a difference in the decline of shockable initial rhythm between OHCAs occurring at a residential location and those at public locations. We included a total of 19 054 OHCA cases and showed that during the total study period (2006-2015), the proportion of shockable initial rhythm declined from 42% to 37%, and this decline was primarily observed in OHCAs at residential locations. When limiting the analysis to more recent study years (2011-2015), the proportion of shockable initial rhythm remained stable (38% to 37%). We also showed that when the time from EMS-call to defibrillator connection time was short (8-10 minutes), the proportion of shockable initial rhythm was still high with 41% for OHCA at a residential location and 71% for OHCA in a public location.

Part 2: The use of automated external defibrillators and new technologies

Chapter 3

In chapter 3 we investigated whether the presence of a system dispatching first responders (firefighters, police officers, and citizen responders) with AEDs may contribute to differences in survival between European regions. We investigated and compared the proportion of ROSC and survival in the total population and the Utstein comparator group (patients with a shockable initial rhythm and a witnessed OHCA). We showed that European regions dispatching first responders (either dispatching one type alone or more than one type) have significant higher ROSC (36% vs. 24%) and OHCA survival rates (total population: 13% vs. 5%, comparator group: 33% vs. 18%) when compared to regions that do not dispatch first responders. We estimated what the theoretical increase would be if a first responder system would be introduced in a region without first responders and showed the potential expected higher survival rate.

Chapter 4

In chapter 4 we determined how often a shockable heart rhythm was stored only in an AED and in such situations, how often information that a shockable rhythm had been present did not reach the treating physician at the hospital. We showed that in 11-13% of OHCAs, a shockable rhythm was only present during the AED connection and that in the majority of cases this information was transferred correctly to the EMS personnel and subsequently from the EMS personnel to the treating physician in the admitting hospital. However, we also showed that adequate transfer to the physician of vital AED information was not always accomplished. In 16% of the cases in our study, the physician was not aware of the AED connection before EMS arrival and in two of these cases, the physician was also not aware of a shockable rhythm during the resuscitation attempt. In one case after receiving the AED ECG the original diagnosis was revised and the patient received the correct treatment. These results likely overestimated the proportion of adequate transfer to the physician of AED defibrillation. In the study region, ARREST personnel has been sending AED information to treating physicians if it was noted that a shockable rhythm was only recorded by the AED, for several years before the present study. Hence, treating physicians in the study region were more primed to the importance of AED information for patient diagnosis and treatment.

Chapter 5

In chapter 5 we examined the new AED algorithm (cprINSIGHT), which analyzes ECG and impedance signals during chest compressions, allowing rhythm analysis with ongoing chest compressions. We assessed the diagnostic accuracy and clinical benefit of the algorithm compared to a conventional AED algorithm. We analyzed data from 465 control (conventional AED) and 425 intervention (AED with cprINSIGHT) cases. We showed that an AED with the cprINSIGHT algorithm has the ability to perform rhythm analysis during chest compressions and could make a shock/no-shock decision during chest compressions 70% of analyses. When the device reached a shock or no-shock decision, the accuracy was high with a sensitivity of 96% (LCL 93%) for shockable rhythms and specificity of 98% (LCL 97%) for non-shockable rhythms. We determined that compared to a conventional AED the use of this new algorithm led to a significantly higher chest compression fraction (86% vs. 80%) and shorter pre-shock pauses (8 sec vs. 22 sec). Although we did not study survival in this study, it can be expected that the improved chest-compression fraction and reduced pre-shock pauses have a positive impact on survival.

Part 3: EMS decision when to transport with ongoing CPR

Chapter 6

In chapter 6 we studied the association between the duration of resuscitation on scene and survival in OHCA patients who did not achieve ROSC on-site and needed to be transported with ongoing CPR. We analyzed the years 2012-2016 and included 655 OHCA patients who were transported with ongoing CPR. We showed that in OHCA patients transported with ongoing CPR, the survival rate significantly declined when time on scene increased. Survivors had a significantly shorter time on scene (20 min vs. 26 min), with the highest survival rate (8%) in patients transported within 20 minutes. We also showed that patients with a shockable rhythm as the first monitored rhythm and patients with a shockable rhythm at the moment of transport had the highest probability to survive 30 days, respectively 7% and 8%.

Chapter 7

In chapter 7 we assessed the rate and time of prehospital ROSC and 30-day survival and studied the optimal timing of the decision to initiate transport without ROSC. We showed that of 810 included patients with prehospital ROSC, 332 (41%) survived 30 days. We determined that survivors had a significantly shorter time-to-ROSC compared to non-survivors (5 vs. 12 min) and 90% of survivors achieved ROSC within 15 minutes compared to 22 minutes of non-survivors. We calculated statistically the most optimal time point using a ROC curve and showed that 8 minutes was the timepoint with the best test performance. When we considered both the benefit of achieving ROSC on scene and the benefit of early transport if ROSC cannot be achieved, our time to ROSC analyses indicated that the best time for the decision to transport appears to be between 8 and 15 minutes after EMS arrival.

Chapter 8

In chapter 8 we explored medical and nonmedical factors that contributed to the EMS decision to transport or terminate the resuscitation on scene and assessed the differences between patients without ROSC transported to the hospital and patients where the resuscitation is terminated on scene. We used both quantitative (OHCA dataset) and qualitative (interviews with paramedics) data. We showed that of 5870 OHCA patients, 3190 (54%) patients did not achieve ROSC on scene. Factors in the quantitative data that were associated with transport (lower age, public location, bystander witnessed arrest, EMS witnessed arrest, and first rhythm VF/VT) only explained 36% of the variance in the decision to transport without ROSC. The additional variance could be explained by findings of our qualitative research in which we identified factors related to the patient, to local circumstances, to the paramedic himself, and to the structure of the organization as important additional themes contributing to the decision to transport a patient with ongoing CPR.

Nieuwe technologieën en besluitvorming tijdens reanimaties buiten het ziekenhuis

Nederlandse samenvatting

In dit proefschrift hebben we onderzoek gedaan naar een schokbaar beginritme, basale reanimatie, gebruik van een automatische externe defibrillator (AED) door 'first responders' (politie, brandweer of burgerhulpverleners) en professionele reanimatie door ambulance medewerkers. We hebben gekeken naar de invloed van AED gebruik en bepaald wat de klinische voordelen zijn van nieuwe technologie in AED's. Verder hebben we door middel van dit proefschrift meer inzicht gekregen in patiënten zonder terugkeer van de circulatie die al reanimerend getransporteerd zijn en de besluitvorming van ambulance medewerkers tijdens een reanimatie.

Deel 1: Optreden van schokbaar eerste beginritme

Hoofdstuk 2

In hoofdstuk 2 hebben we onderzoek gedaan naar de proportie schokbaar beginritme en of deze nog steeds dalende is over een periode van 10 jaar. Hiervoor hebben we data gebruikt van meerdere ambulancediensten uit 4 verschillende Europese landen (Denemarken, Noorwegen, Zweden, Nederland). Verder hebben we onderzoek gedaan of er een verschil is in de proportie schokbaar beginritme bij patiënten met een hartstilstand in of om het woonhuis ten opzichte van patiënten met een hartstilstand in een openbare locatie. We hebben in totaal 19 054 patiënten geïncludeerd en aangetoond dat de proportie schokbaar beginritme gedaald is van 42% naar 37% en dat deze daling vooral geobserveerd werd bij patiënten met een hartstilstand in of om het woonhuis. Wanneer we de analyse beperken tot de recentere studie jaren (2011-2015) bleek dat de proportie schokbaar eerste beginritme stabiel bleef (38% naar 37%). Verder hebben we laten zien dat wanneer de tijd tot aansluiten van een defibrillator kort is (8 tot 10 minuten), de proportie schokbaar beginritme nog steeds hoog is, 41% bij patiënten met een hartstilstand in of om het woonhuis en 71% bij patiënten met een hartstilstand in een openbare locatie.

Deel 2: Het gebruik van automatische externe defibrillatoren (AED) en nieuwe technologieën

Hoofdstuk 3

In hoofdstuk 3 hebben we onderzoek gedaan of de aanwezigheid van een first responder systeem met de inzet AED's bijdraagt aan het verschil in overleving tussen Europese regio's. We onderzochten en vergeleken het percentage van patiënten met ROSC en de overleving in de totale populatie en de Utstein vergelijkingsgroep (patiënten met schokbaar eerste ritme en een getuige van de hartstilstand). We hebben aangetoond dat Europese regio's die first responders inzetten (zowel één type als meer dan één type) een significant hogere proportie ROSC (36% vs. 24%) en overleving (totale populatie 13% vs. 5% en vergelijkingsgroep 33 vs. 18%) hebben vergeleken met regio's die geen first responders uitzenden. We hebben een inschatting, door middel van een theoretische berekening, gemaakt wat de stijging in overleving zou zijn wanneer een first responder systeem zou worden geïntroduceerd en hebben laten zien dat er dan een hogere overleving verwacht kan worden.

Hoofdstuk 4

In hoofdstuk 4 hebben we bepaald hoe vaak een schokbaar hartritme alleen in een AED was opgeslagen en hoe vaak, in zo'n situatie, de informatie dat er een schokbaar hartrtime was niet bij de behandelend arts in het ziekenhuis terecht kwam. We hebben aangetoond dat in 11-13% van alle reanimaties buiten het ziekenhuis een schokbaar hartritme alleen maar zichtbaar was gedurende de AED connectie en dat in de meerderheid van die patiënten de informatie correct naar het ambulance personeel was overgedragen en daarop volgend van ambulance personeel naar de behandelend arts in het ziekenhuis. Echter, we hebben ook aangetoond dat adequate overdracht van vitale AED informatie niet altijd bij de behandelend arts terecht kwam. In 16% van alle casussen in onze studie was de behandelend arts niet op de hoogte van het schokbare ritme tijdens de reanimatie. In één casus werd de oorspronkelijke diagnose herzien na het ontvangen van het ECG van de AED en ontving de patient de correcte behandeling. Deze resultaten geven mogelijk een overschatting van hoe vaak de informatie uit de AED dat er een schokbaar hartrtime was adequaat werd overgedragen aan de arts. Het is namelijk zo dat in de jaren voorafgaand aan deze studie het ARREST personeel in onze studie regio de AED informatie heeft verstuurd naar de behandelend arts als een schokbaar hartritme alleen in een AED was opgeslagen,. Hierdoor zijn de artsen in de regio mogelijk meer ingesteld op het belang van AED informatie voor de juiste diagnose en behandeling van een patient.

Hoofdstuk 5

In hoofdstuk 5 hebben we een nieuw AED algoritme (cprINSIGHT) onderzocht, welke het ECG (hartfilmpje) analyseert tijdens borstcompressie waardoor het mogelijk is het hartritme te analyseren zonder de borstcompressie te onderbreken. We hebben de diagnostische nauwkeurigheid beoordeeld en de klinische voordelen vergeleken met een standaard AED algoritme. We hebben data geanalyseerd van 465 controle (standaard AED) en 425 interventie (AED met cprINSIGHT) casussen. We hebben aangetoond dat een AED met cprINSIGHT het vermogen heeft om het hartritme te analyseren tijdens de borstcompressie en een schok/geen schok beslissing kan maken tijdens borstcompressie in 70% van alle AED analyses. Wanneer de AED tot een schok/geen schok beslissing kwam, was de nauwkeurigheid hoog met een sensitiviteit van 96% voor schokbare ritmes en specificiteit van 98% voor niet schokbare ritmes. We hebben vastgesteld dat vergeleken met een standaard AED, het gebruik van een AED met cprINSIGHT leidt tot een significant hogere borstcompressie fractie (86% vs. 80%) en kortere pauzeduur voor toedienen van de schok (8 sec vs. 22 sec). Hoewel we niet naar overleving hebben gekeken in deze studie, kunnen we verwachten dat verhoging van de borstcompressie fractie en kortere pauzeduur voor toedienen van de schok een verbetering van de overleving kan geven.

Deel 3: Besluitvorming ter plaatse, wanneer al reanimerend te transporteren

Hoofdstuk 6

In hoofstuk 6 hebben we gekeken naar de associatie tussen de duur van de reanimatie ter plaatse en overleving in patiënten met een hartstilstand die al reanimerend zijn getransporteerd naar het ziekenhuis. We hebben de jaren 2012-2016 geanalyseerd en 655 patiënten die al reanimerend zijn getransporteerd geïncludeerd. We hebben laten zien dat de overlevingskans significant afnam naarmate de reanimatieduur ter plaatse voor transport toenam. Overlevers hadden een significant kortere reanimatieduur ter plaatse (20 min vs. 26 min) met de hoogste overleving (8%) in de groep patienten die getransporteerd werd binnen 20 minuten. We hebben ook aangetoond dat patiënten met een schokbaar beginritme en patiënten met een schokbaar ritme ten tijde van transport, de hoogste kans hebben te overleven, respectievelijk 7% en 8%.

Hoofdstuk 7

In hoofdstuk 7 hebben we de proportie en tijd tot 'terugkeer van de circulatie' (ROSC) voor aankomst van het ziekenhuis (prehospitaal) en 30-dagen overleving beoordeeld en onderzoek gedaan naar de optimale tijd voor het besluit tot starten met transporteren zonder ROSC. We hebben laten zien dat van 810 geincludeerde patiënten met prehospitaal ROSC, 332 (41%) overleefde. We hebben aangetoond dat overlevers een significant kortere tijd tot ROSC hadden vergeleken met patiënten die zijn overleden (5 min vs. 12 min) en dat 90% van de overlevers ROSC had binnen 15 minuten in vergelijking met 22 minuten voor patiënten die zijn overleden. We met behulp van statistiek (ROC curve) berekend wat het optimale tijdspunt voor start van transport zou zijn en daaruit bleek 8 minuten het tijdspunt met de beste test eigenschappen. Wanneer we zowel het voordeel van streven naar ROSC ter plaatste als het voordeel van vroeg transporteren zonder ROSC in acht nemen, wijzen onze analyses erop dat de beste tijd voor het besluit om te transporteren tussen de 8 en 15 minuten na aankomst van de ambulance ligt.

Hoofdstuk 8

In hoofdstuk 8 hebben we onderzoek gedaan naar medische en niet medische factoren die bijdragen aan het besluit om een patiënt al reanimerend te transporteren, dan wel de reanimatie te termineren ter plaatse en de verschillen tussen deze twee patiëntengroepen in kaart te brengen. We hebben gebruik gemaakt van zowel kwantitatieve (dataset) als kwalitatieve (interviews) data. We hebben laten zien dat van 5780 patiënten met een hartstilstand, 3190 (54%) patiënten geen ROSC kregen ter plaatse. De factoren die in de kwantitatieve dataset geassocieerd waren met transport (leeftijd, publieke locatie, omstander getuige, ambulance getuige, schokbaar eerste beginritme) verklaarden slechts 36% van de variantie in het besluit tot transporteren zonder ROSC. De additionele variantie kan mogelijk verklaard worden door onze bevindingen in het kwalitatieve ondezoek. Hieruit kwamen factoren gerelateerd aan de patiënt, lokale omstandigheden, de ambulance verpleegkundige en de structuur van de organisatie naar voren als belangrijke thema's bijdragend in het besluit om een patient al reanimerend te transporteren.

Discussion and future perspectives

Part 1: Occurrence of shockable initial rhythm

The introduction or extension of AED initiatives is still worthwhile

We found that the occurrence of shockable initial rhythm stabilized, particularly in OHCAs occurring at a residential location, during the 5 most recent years studied. The decline present in the first 5 years of the study may result from an absolute decrease of patients at risk for a shockable initial rhythm (primary prevention measures, improved treatment, and ICD use) or from an absolute increase in non-shockable rhythms (population changes, such as patients with higher age and more comorbidities).[1-4] The stabilization of the proportion of a shockable initial rhythm may, at least partly, be a result of an increasing rate of bystander CPR and AED defibrillation (figure 1).

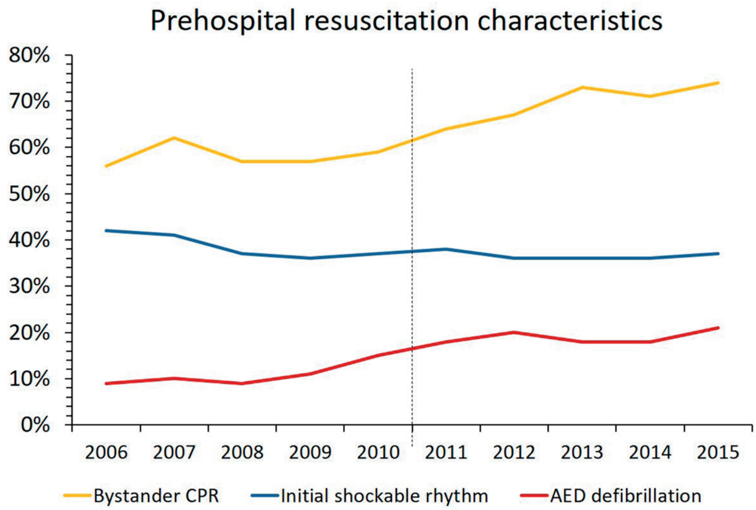


Figure 1. Prehospital resuscitation characteristics and shockable initial rhythm

Bystander CPR includes all CPR performed before the arrival of EMS. CPR can be performed by local bystanders such as family or witnesses of an arrest in public or by dispatched first responders (police, firefighters, or citizen-responders). The increase in bystander CPR can be explained by the increasing use of first responders (police, firefighters, or citizen-responders) through the years who are being dispatched with AEDs before EMS arrival. Increased chance of receiving bystander CPR reduces the no-flow time because CPR is started earlier, which may lead to slower degeneration of a shockable initial rhythm.[5,6] Also, the use of AEDs before EMS arrival results in a shorter time from collapse to connection and registration of the heart rhythm resulting in a higher proportion of shockable initial rhythm because not enough time has passed for the rhythm to degenerate into asystole.

OHCA patients at a residential location differ unfavorably from OHCA patients in a public location.[7,8] However, we showed that the observed decline in shockable initial rhythm has stabilized, particularly in OHCAs occurring at a residential location and the proportion of shockable initial rhythm is still high when there is a short delay (10 minutes or less) between EMS-call and defibrillator connection. In addition, we know from the literature that the use of AEDs at a residential location decreases the time from EMS-call to defibrillator connection and is associated with increased survival.[9] With 70% of OHCAs occurring at a residential location and survival rates significantly lower than OHCA occurring in public places[10] we recommend the continuous effort to improve resuscitation care at residential locations by introducing or extend AED initiatives to facilitate early defibrillation, to help improve the survival.

Part 2: The use of automated external defibrillators and new technologies

Dispatching first responders with AEDs can improve survival

Dispatching first responders (police, firefighters, or citizen-responders) with AEDs before the arrival of EMS is a strategy to improve resuscitation care. We found that survival rates in European regions with a first responder system that dispatches first responders were higher in the total population and the Utstein comparator group compared to European regions without first responders. We know from previous literature that the use of an AED before the arrival of EMS reduces the time from call to defibrillation and therefore increases the survival chances of OHCA patients with a shockable initial rhythm.[9,11,12] So the main impact of dispatching first responders with AEDs is seen in patients with a shockable initial rhythm.[13] Not only the use of first responders but also the implementation of a first responders system, especially a system that uses citizen responders, could have multiple effects on a region or neighbourhood and help improve resuscitation outcomes. It could be that the introduction of a first responder system causes increased public awareness of the need for bystander CPR in the case of an OHCA. A higher awareness due to the implementation of a first responder system might be associated with a higher likelihood of also non-dispatched bystander CPR and subsequently, favourable survival outcomes after OHCA.[14] For example, people hearing of their neighbours, family, or friends being trained and dispatched as citizen responders might be more positive towards performing CPR themselves in case of an OHCA. We favour the introduction of first responder systems in European regions without first responder to improve resuscitation care and survival.

The need of transferring AED information to the hospital

Due to public programs, AED initiatives, and implementation of first responder systems, defibrillation in OHCA is increasingly performed by bystanders and dispatched first responders before the arrival of EMS, using AEDs.[15-18] So the initial heart rhythm is increasingly registered in AEDs and no longer in EMS manual defibrillators.[19] We found that in 26-29% of the analyzed resuscitation attempts an AED defibrillated before the arrival of EMS and in 11-13% of the OHCAs only the AED delivered shocks and no further defibrillation was needed by EMS. In 6-9% of OHCA cases, EMS data did not mention a shockable rhythm and in 3-4% of cases, the treating physician was not aware of a shockable rhythm. AED information is not routinely downloaded and made available for patient diagnosis, and treatment so usually the treating physicians have no access to ECGs from AEDs. The initial heart rhythm is important for diagnosis, clinical decision-making, and patient treatment.[20] Information such as type of shockable rhythm (VF or VT), is a key element when implantation of an ICD is considered.[21] Also in patients with a non-shockable rhythm, the ECG from the AED can be helpful for clinical decision making and correct patient treatment, for example, a shock delivered on atrial fibrillation or due to an operator-related error (figure 2).[22,23]

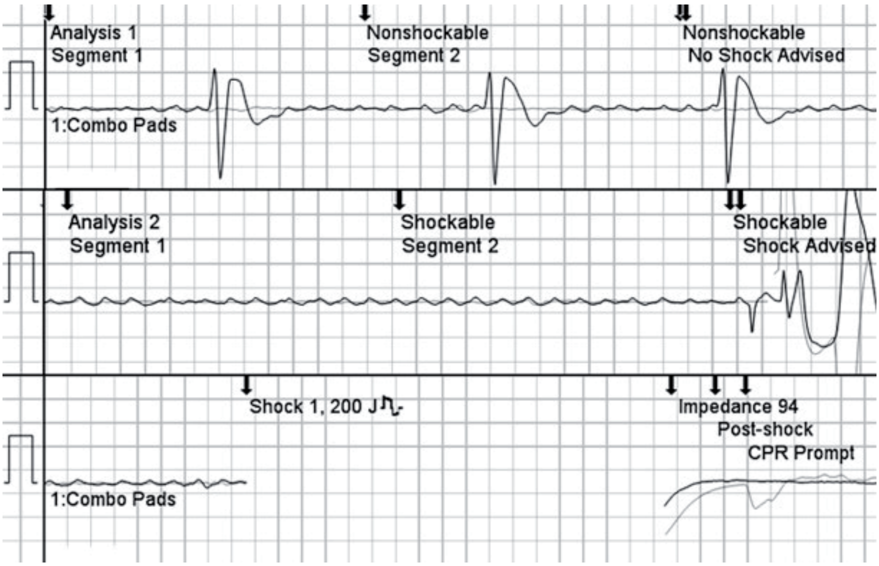


Figure 2. Electrocardiogram of automated external defibrillator showing initial rhythm assessment (panel 1), and second rhythm check after two minutes (panel 2) resulting in a shock (panel 3) from Hulleman et al.(21)

Due to the hectic setting of an OHCA and the multiple information transfers moments in the chain of care the correct information about the presence of an AED shock is easily lost. We want to recommend establishing an organized infrastructure to register AED use during OHCAs, so adequate transfer of AED information to the treating physician can be realized and be available for the diagnosis and treatment of OHCA patients. One of the possibilities to realize this is creating a national AED registry where a treating physician can retrieve the AED data of OHCA patients. Another possibility is an infrastructure where the AED data can be automatically sent to the EMS services or treating hospital so the AED data is immediately available for both EMS and treating physicians. Currently, it is difficult to create such infrastructure because there are different AED brands, with different software systems and ECG data download possibilities generally not available for EMS or hospitals. Furthermore, AEDs can be privately bought and owned by organizations and companies which may result in difficulty in retrieving AED data, different opinions on ownership of AED data, privacy regulations, and fear of losing the company property.[24]

AED analysis during chest compressions has clinical benefit

Besides improving the adequate transfer of AED information to the treating physician, the AED technology itself can also be improved. We found that AED devices with a new algorithm (cprINSIGHT) can perform rhythm analysis during chest compressions and that in comparison with conventional AEDs the use of this new algorithm leads to a significantly higher chest compression fraction (CCF) and shorter pre-shock pauses. Other studies have shown the potential benefit of different algorithms in analyzing the ECG during chest compressions in test datasets and simulated OHCA but clinical experience on OHCA patients with these algorithms is not yet reported.[25-30] Our study is the first clinical study on a new algorithm installed in an AED and used in OHCA, making the results representative of the clinical performance during AED use by rescuers. To estimate the clinical benefit for the patient we need to know how chest compression fraction and pre-shock pause influence the outcome. Previous observational studies have found inconsistent results on the associations between CCF and survival. Some studies have shown that a higher CCF was independently associated with better survival,[31,32] while other studies did not show such an association.[33-35] Previous published studies on pre-shock pauses found that shorter pre-shock pauses were associated with better survival.[36-39] When we take the previously published literature into account we can expect that the increase in CCF (86% vs 80%) and the decrease in pre-shock pause (8 sec vs 22 sec) as found in our study to be favorable for survival. The next step could be heart rhythm analysis during chest compressions in a continuous mode, which immediately identifies a shockable rhythm the moment it occurs or recurs after initial termination. This will shorten the time between the occurrence/recurrence of a shockable rhythm and delivery of a shock because there is no need to await the end of the full two-minute cycle until a protocolized rhythm check. In addition to AEDs, rhythm analysis during chest compressions could also be implemented in EMS manual defibrillators, although the hands-off time for rhythm analysis is usually much shorter compared to AEDs. This technology could help EMS to also increase the chest compression fraction and shorten the pre-shock pauses.

Part 3: EMS decision when to transport with ongoing CPR

The decision to transport needs to be made early in the resuscitation process

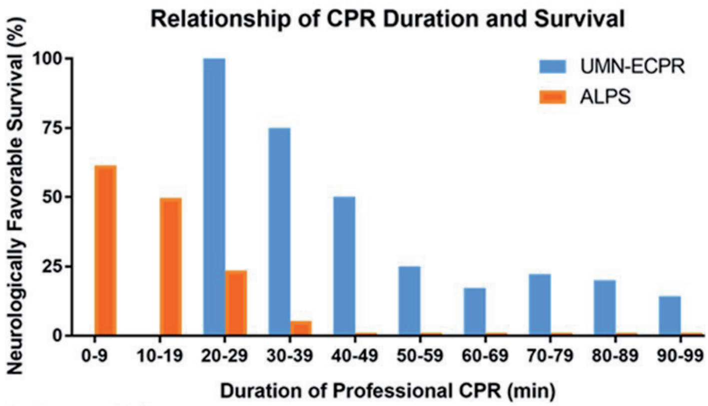
Another link in the chain of survival of OHCA is the advanced life support (ALS) treatment delivered by EMS. When a patient does not achieve ROSC despite ALS, EMS can decide to either transport the patient with ongoing CPR or terminate the resuscitation on scene.[40] We found that In OHCA patients transported with ongoing CPR the survival rate significantly declines when the time of resuscitation on scene before transport increases. Also, we found that In OHCA patients with prehospital ROSC survival significantly decreases with increasing time-to-ROSC. Our time to ROSC analyses indicated that the best time for the decision to transport appears to be between 8 and 15 minutes after EMS arrival if ROSC is not yet achieved. ERC and AHA guidelines generally accept withdrawing further resuscitation, in case of asystole for more than 20 minutes during ALS on scene. We recommend that the decision to transport for all patients that may meet certain criteria must clearly be made early in the resuscitation process and well before termination is even considered.

Transport with ongoing CPR needs to be safe and ensure the quality of CPR

At the beginning of resuscitation, it is not known which patients will achieve ROSC and at what time. We do not know whether the chances of achieving ROSC are different in patients who were transported without ROSC compared with the same type of patients in which the resuscitation was continued on scene. Transporting a patient with ongoing CPR is associated with interruptions in CPR and a possible lower survival rate.[36,41,42] Also, performing manual CPR in a moving ambulance reduces the quality of CPR and is potentially harmful to the paramedic.[43,44] So to facilitate and support earlier transport in patients without ROSC, the quality of CPR and safety of the paramedics during transport needs to be ensured, the use of mechanical CPR could facilitate this.[43,45]

The need for novel treatment strategies in the hospital when conventional therapy fails

When resuscitation efforts on scene fail there is a need for a treatment strategy in the hospital that cannot be done in the prehospital setting. The treatment strategy has to be sufficiently beneficial for patients without ROSC to exceed the "cost" of transport. The use of extracorporeal cardiopulmonary resuscitation (ECPR) in OHCA is a new strategy, which could improve the chances of survival in a selected group of OHCA patients.[46] Recently results of the first randomized clinical trial in the USA of extracorporeal membrane oxygenation (ECMO) compared to standard ACLS treatment in patients with OHCA and refractory VF were published.[47] In this study, 30 patients were randomly assigned to standard ACLS treatment (n=15) or early ECMO-facilitated resuscitation (n=15), survival to hospital discharge was observed in one (7%) of the patients in the standard ACLS treatment group versus six (43%) of the patients in the ECMO-facilitated group. Although the number of included patients was small, early ECMO-facilitated resuscitation significantly improved survival to hospital discharge of patients with refractory VF compared with standard ACLS treatment. Randomized studies are lacking, however, there are multiple observational studies comparing ECPR to historical controls and case-matched controls show promising results in favor of ECPR.[48-50] Patients without ROSC almost always achieve normal heart rhythm after ECPR initiation but neurological outcome so far remains unpredictable, although there is evidence that patients with shorter low-flow duration, shockable cardiac rhythm, higher arterial pH value, and lower serum lactate concentration on hospital admission are more likely to have a favorable neurologic outcome.[51] Recently, another observational study was published comparing two groups of patients with refractory VF/VT, a cohort of patients treated according to an ECPR protocol, and a comparison cohort of patients who received standard CPR.[52] In this study ECPR was associated with improved neurologically favorable survival at all CPR durations <60 minutes (figure 3).



Patients at Risk

Time (min)	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99	Total
UMN-ECPR	0	0	8	12	20	36	35	27	15	7	160
ALPS	70	151	102	95	99	69	29	11	3	7	636

Figure 3. Relationship of CPR duration and survival. Figure from Bartos Jason et al. Circulation 2020 (52)

More randomized controlled trials are needed to show the clinical benefit with a high level of evidence, therefore recently the INCEPTION trial, a multicenter, randomized controlled trial, was designed to evaluate the effectiveness of ECPR.[53] Patients in this trial are allocated to either continued CPR or ECPR. Patients eligible for inclusion are adults (≤ 70 years) with witnessed OHCA presenting with a shockable initial rhythm (VF/VT), who received bystander CPR, and who fail to achieve ROSC within 15 minutes of ALS by EMS (figure 4).

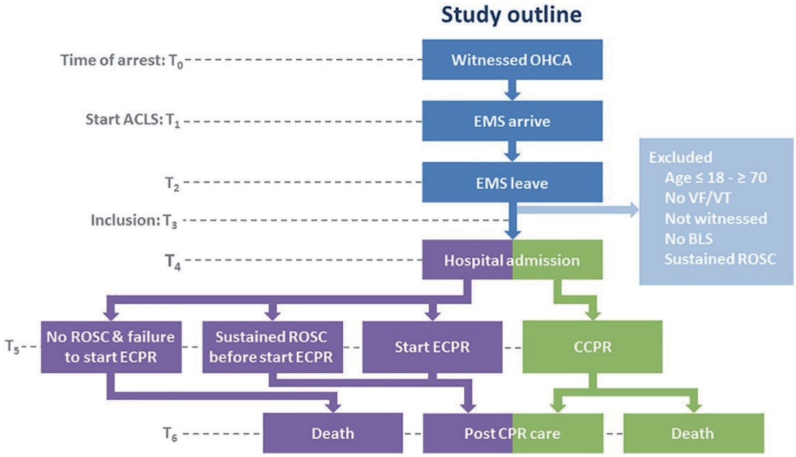


Figure 4. INCEPTION trial study outline. Figure from Bol et al., American Heart Journal 2019 (53)

Patients are also excluded when it is estimated that cannulation will start 60 minutes after the initial arrest. These in- and exclusion criteria have some drawbacks that have to be taken into account. First, the location of the OHCA cannot be standardized and therefore impacts on the possibility of early transport, for example, if a patient is on the fifth floor EMS has to wait for firefighters to get the patient out of the building. Furthermore, if the OHCA is in a rural region the transport time to the hospital can be much longer compared to urban regions. Both these factors influence the possibility of an ECPR cannulation within 60 minutes after the initial arrest. Instead of transport to the hospital for ECPR, another possibility is to bring ECPR to the patient. Some studies have proven that it is feasible to provide prehospital ECPR to minimize low flow time.[48] At the moment ECPR is not a standard treatment and requires fully trained staff that are readily available upon the decision to transport the patient to the hospital. In the case of pre-hospital ECPR, the staff also needs to be available to be dispatched to an OHCA site and perform ECPR without the facilities of a hospital which could potentially introduce problems such as availability of staff, logistics, and creation of a sterile work environment outside the hospital. Currently, it is unclear if the provision of prehospital ECPR is superior or inferior to the transport of the OHCA patient to a center that provides ECPR and if it is more or less cost-effective (if at all) than in-hospital ECPR. We are looking forward to the first results of randomized studies which will help to clarify if ECPR is a beneficial treatment for patients who do not respond to conventional resuscitation efforts. Enrolment in the Inception trial is completed and results are expected shortly.

Importance of additional factors contributing to the decision-making on scene

The studies described in this thesis are all performed with study data from a period where there were no hospitals in the region that used ECPR as a treatment strategy in OHCA patients. Nonetheless, a proportion of patients without ROSC were transported with ongoing CPR to the hospital. We found that from the quantitative data it remains unclear why a patient is transported with ongoing CPR in some situations, but the resuscitation is terminated in others. With qualitative research, we found that multiple factors contribute to the decision-making on scene such as age and comorbidities of the patient, pressure by family or bystanders, the safety of the OHCA location, work experience of the paramedic, the experience of an incident or lawsuit, and the availability of mechanical CPR. We underline the importance of these additional factors in the decision-making on scene and the necessity to give more attention to end-of-life decision-making experiences of paramedics and communication with bystanders or family.

Recommendation for further OHCA research

Rhythm analysis during chest compressions and survival

We recommend to assess the clinical benefit of rhythm analysis on an outcome level such as survival. Therefore, a very different study design, preferably a randomized study, and far greater numbers of patients would be required. In the acute setting of an OHCA, randomization may be difficult to facilitate because not every AED or AED user encounters the same number of OHCAs, so random allocation of which mode (standard vs rhythm analysis during chest compressions) per device or user is complicated. Also, defibrillation is done by AEDs and by EMS defibrillators, that are not yet equipped with such analysis algorithms. Furthermore, to study an outcome as survival a large number of OHCA patients are needed to include enough patients with a shockable rhythm and survivors to compare and provide enough power to determine whether a difference is statistically significant. For example, if we hypothesize that the overall OHCA survival due to rhythm analysis during chest compressions will increase by 5% (from 25% to 30%), the sample size for each group will be more than 1000 OHCA patients. In the Arrest study region, there are approximately 900-1000 OHCA patients with presumed cardiac arrest per year. Taking into account that the AED connection rate proportion is ≈66% (including public AEDs and first responder AEDs) and that the proportion of patients with a shockable rhythm is ≈35%, a randomized study will therefore take multiple years of inclusion. Although a randomized study would be the preferred study design, some next steps can be taken in the setting of a prospective observational study. Prehospital outcome measures such as ROSC can be historically compared, preferable comparing subsequent periods of the same AED users in the same region, to minimize user and regional differences. Also, the use of an AED with improved technology is only one link in the chain of survival of OHCA future research has to take EMS, resuscitation, patient, and hospital characteristics into account.

Which patients without ROSC need to be transported to the hospital

As discussed before the use of ECPR in OHCA is a promising new strategy. However, at the moment randomized studies are still ongoing and only a selected group of OHCA patients are included and seen as eligible for ECPR. The question remains what is the optimal time for the decision to transport and for which patients in refractory arrest transport is beneficial. We recommend randomized trials on early vs. later transport without ROSC to elucidates this, although this could be difficult in the daily clinical practice of an OHCA because early transport relies on multiple factors such as the location of the patient (home vs public) and availability of mechanical CPR to guarantee the quality of CPR and safety of the paramedic during transport. Furthermore, current studies focus on the group of patients with a shockable rhythm and refractory arrest as eligible patients for ECPR. There is evidence that some patients with a non-shockable rhythm could also benefit from ECPR, in particular patients with a pulmonary embolism.[54,55]

Quantification of contributing factors in the daily practice of decision making on scene

We recommend further research on how often in daily practice a factor will contribute to the decision. Our data can be used to further explore to what extend other factors quantitatively contribute to the decision to either transport or terminate a resuscitation. If specific factors do quantitatively contribute to the decision the next step will be to evaluate if it is necessary to include these factors in training or guidelines.

Conclusion

The links in the chain of OHCA survival keep improving. The use of AEDs and first responders before EMS arrival results in decreasing time to defibrillation and increasing the survival chances of OHCA patients. When an AED is used, the vital AED information on the initial rhythm needs to be transferred to the treating physician to optimize patient treatment. New technology in AEDs that can analyze the heart rhythm during chest compressions has the potential to improve resuscitation care before EMS arrival even more. Still, when despite all the resuscitation efforts an OHCA patient does not achieve ROSC a decision has to be made. Multiple factors contribute to the decision to transport a patient or terminate the resuscitation on scene. Nonetheless, with the upcoming novel treatment strategy ECPR the decision to transport with ongoing CPR (if safely possible with mechanical CPR) should be made early in the resuscitation process to increase the chances of survival.

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A

APPENDICES

Appendices

List of publications

Included in this thesis

- de Graaf C*, Oving I*, Karlsson L, Jonsson M, Kramer-Johansen J, Berglund E, Hulleman M, Beesems SG, Koster RW, Olasveengen TM, Ringh M, Claessen A, Lippert F, Hollenberg J, Folke F, Tan HL, Blom MT. Occurrence of shockable rhythm in out-of-hospital cardiac arrest over time: A report from the COSTA group. *Resuscitation. 2020; 151: 67-74*
  *both authors contributed equally

- Oving I, de Graaf C, Masterson S, Koster RW, Zwinderman AH, Stieglis R, Alihodzic H, Baldi E, Betz S, Cimpoesu D, Folke F, Rupp D, Semeraro F, Truhlar A, Tan HL, Blom MT. European First Responder systems and differences in return of spontaneous circulation and survival after out-of-hospital cardiac arrest: a study of registry cohorts. *The Lancet Regional Health - Europe. 2021; 1: 100004*

- Homma PCM, de Graaf C, Tan HL, Hulleman M, Koster RW, Beesems SG, Blom MT. Transfer of essential AED information to treating hospital (TREAT). *Resuscitation. 2020; 149: 47-52*

- de Graaf C, Beesems SG, Oud S, Stickney RE, Piraino DW, Chapman FW, Koster RW. Analyzing the heart rhythm during chest compressions: performance and clinical value of a new AED algorithm. *Resuscitation. 2021; 162: 320-328*

- de Graaf C, Beesems SG, Koster RW. Time of on-scene resuscitation in out of-hospital cardiac arrest patients transported without return of spontaneous circulation. *Resuscitation. 2019; 138: 235-242*

- de Graaf C, Donders DNV, Beesems SG, Henriques JPS, Koster RW. Time to Return of Spontaneous Circulation and Survival: When to Transport in out-of-Hospital Cardiac Arrest? *Prehospital Emergency Care. 2020; 7: 1-11*

- de Graaf C, de Kruif ATCM, Beesems SG, Koster RW. To transport or to terminate resuscitation on-site. What factors influence EMS decisions in patients without ROSC? A mixed-methods study. *Resuscitation. 2021; 164: 84-92*

Not included in this thesis

- Andelius L*, Oving I*, Folke F, de Graaf C, Stieglis R, Kjoelbye JS, Hansen CM, Koster RW, L Tan H, Blom MT; ESCAPE-NET investigators. Management of first responder programmes for out-of-hospital cardiac arrest during the COVID-19 pandemic in Europe. *Resusc Plus 2021; 5: 100075.*
  *both authors contributed equally

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Author contributions to the published work

For all chapters:

**both authors contributed equally*
All authors approved the final version that was submitted.

Chapter 2

de Graaf C*, Oving I*, Karlsson L, Jonsson M, Kramer-Johansen J, Berglund E, Hulleman M, Beesems SG, Koster RW, Olasveengen TM, Ringh M, Claessen A, Lippert F, Hollenberg J, Folke F, Tan HL, Blom MT. Occurrence of shockable rhythm in out-of-hospital cardiac arrest over time: A report from the COSTA group. *Resuscitation. 2020; 151: 67-74*

Corina de Graaf: study design, data collection, data analysis, data interpretation, writing manuscript, figures and tables.
Iris Oving: study design, data collection, data analysis, data interpretation, writing manuscript, figures and tables.
Lena Karlsson: data collection data interpretation, review manuscript
Martin Jonsson: data collection data interpretation, review manuscript
Jo Kramer-Johansen: data collection data interpretation, review manuscript
Ellinor Berglund: data interpretation, review manuscript
Michiel Hulleman: data interpretation, review manuscript
Stefanie Beesems: data interpretation, review manuscript
Rudolph Koster: data interpretation, review manuscript
Theresa Olasveengen: data interpretation, review manuscript
Mattias Ringh: data interpretation, review manuscript
Andreas Claessen: data interpretation, review manuscript
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Marieke Blom: study supervisor, study design, data analysis, data interpretation, writing and review of manuscript

Chapter 3

Oving I, de Graaf C, Masterson S, Koster RW, Zwinderman AH, Stieglis R, Alihodzic H, Baldi E, Betz S, Cimpoesu D, Folke F, Rupp D, Semeraro F, Truhlar A, Tan HL, Blom MT. European First Responder systems and differences in return of spontaneous circulation and survival after out-of-hospital cardiac arrest: a study of registry cohorts. *The Lancet Regional Health - Europe. 2021; 1: 100004*

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Hajriz AliHodzic: data collection, review manuscript
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Hanno Tan: study design, data interpretation, writing and review of manuscript
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Chapter 4

P.C.M. Homma, C. de Graaf, H.L. Tan, M. Hulleman, R.W. Koster, S.G. Beesems, M.T. Blom. Transfer of essential AED information to treating hospital (TREAT),
Resuscitation. 2020; 149: 47-52

Paulien Homma: study design, data collection, data analysis, data interpretation, writing manuscript, figures and tables
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Hanno Tan: data interpretation, writing and review of manuscript
Michiel Hulleman: data interpretation, review manuscript
Rudolph Koster: data interpretation, review manuscript
Stefanie Beesems: data interpretation, review manuscript
Marieke Blom: study supervisor, study design, data analysis, data interpretation, writing and review of manuscript

Chapter 5

C. de Graaf, S.G. Beesems, S. Oud, R.E. Stickney, D.W. Piraino, F.W. Chapman, R.W. Koster. Analyzing the heart rhythm during chest compressions: performance and clinical value of a new AED algorithm.
Resuscitation. 2021; 162: 320-328

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Ronald Stickney: data interpretation, review manuscript
Daniel Piraino: data interpretation, review manuscript
Fred Chapman: data interpretation, review manuscript
Rudolph Koster: study supervisor, study design, data analysis, data interpretation, writing and review of manuscript

Chapter 6

C. de Graaf, S.G. Beesems, R.W. Koster. Time of on-scene resuscitation in out of-hospital cardiac arrest patients transported without return of spontaneous circulation.
Resuscitation. 2019; 138: 235-242

Corina de Graaf: study design, data collection, data analysis, data interpretation, writing manuscript, figures and tables
Stefanie Beesems: study design, data interpretation, writing and review of manuscript
Rudolph Koster: study supervisor, study design, data analysis, data interpretation, writing and review of manuscript

Chapter 7

C. de Graaf, D.N.V. Donders, S.G. Beesems, J.P.S. Henriques, R.W. Koster. Time to Return of Spontaneous Circulation and Survival: When to Transport in out-of-Hospital Cardiac Arrest? *Prehospital Emergency Care. 2020; 7: 1-11*

Corina de Graaf: study design, data collection, data analysis, data interpretation, writing manuscript, figures and tables
Dominique Donders: data collection, data analysis, data interpretation and review of manuscript
Stefanie Beesems: study design, data interpretation, writing and review of manuscript
Jose Henriques: data interpretation, review manuscript
Rudolph Koster: study supervisor, study design, data analysis, data interpretation, writing and review of manuscript

Chapter 8

C. de Graaf, A.T.C.M. de Kruif, S.G. Beesems, R.W. Koster. To transport or to terminate resuscitation on-site. What factors influence EMS decisions in patients without ROSC? A mixed-methods study
Resuscitation. 2021; 164: 84-92

Corina de Graaf: study design, data collection, data analysis, data interpretation, writing manuscript, figures and tables
Anja de Kruif: study design, data analysis, data interpretation, writing and review of manuscript
Stefanie Beesems: study design, data interpretation, review of manuscript
Rudolph Koster: study supervisor, study design, data analysis, data interpretation, writing and review of manuscript

PhD portfolio

PhD student: C. de Graaf
Supervisor: prof. dr. A.A.M. Wilde, prof. dr. J.P.S. Henriques
Co-supervisors: dr. R.W. Koster, dr. S.G. Beesems
PhD-period: February 2017 - September 2021

1. PhD training

Courses	Year	ECTS
AMC World of Science	2017	0.7
Practical Biostatistics	2017	1.1
Basic Course Legislation and Organization – eBROK	2017	1.0
BLS and AED use instructor	2017	0.8
Scientific Writing in English for Publication	2018	1.5
Oral Presentation in English	2018	0.8
Didactic Skills Training	2018	0.4
Clinical Epidemiology: Observational Epidemiology	2018	0.6
Clinical Epidemiology: Randomized Clinical Trials	2018	0.6
Boerhaave nascholing: Klinische Epidemiologie	2018	2.0
EpidM: cursus Kwalitatief onderzoek in de praktijk van de gezondheidszorg	2018	2.0
Talents in PhD	2019	0.32
Masterclasses		
Masterclass Ethische Dilemma's in de praktijk	2017	3.0
Presentations		
Amsterdam Cardiovascular Sciences Symposium (oral presentation)	2017	0.5
European Resuscitation Council (ERC) Congres (oral presentation)	2017	0.5
European Resuscitation Council (ERC) Congres (poster presentation)	2018	0.5
American Heart Resuscitation Science Symposium (oral presentation)	2018	0.5
American Heart Resuscitation Science Symposium (poster presentation)	2018	0.5
Nederlandse Reanimatie Raad (NRR) Congres (oral presentation)	2019	0.5
European Resuscitation Council (ERC) Congres (oral presentation)	2019	0.5
American Heart Resuscitation Science Symposium (oral presentation)	2019	0.5
National Association of EMS Physicians (NAEMSP) Meeting (oral presentation)	2020	0.5
National Association of EMS Physicians (NAEMSP) Meeting (poster presentation)	2020	0.5
European Resuscitation Council (ERC) Congres (oral presentation)	2021	0.5
(Inter)national conferences		
Euro Elso Congres	2017	0.25
Nederlandse Reanimatie Raad (NRR) Congres	2017 - 2019	0.75
Amsterdam Cardiovascular Sciences Symposium	2017, 2018	0.5
European Resuscitation Council (ERC) Congres	2017 - 2020	3.0
American Heart Resuscitation Science Symposium	2018, 2019	1.0
National Association of EMS Physicians (NAEMSP) Meeting	2020	0.75

2. Teaching

Lecturing	Year	ECTS
ZIGMA avond VUmc	2017	0.1
Reanimatie competitie OLVG-Oost	2017, 2018	0.2
EHBO avond, Broek in Waterland	2017	0.1
Teamdagen Ambulance Witte Kruis	2017	0.1
AMC WIT festival	2018	0.1
Jubileum avond Polderhartstichting, Schermerhorn	2019	0.1
Symposium Acute Cardiologie, Haaglanden MC	2019	0.1
Masterclass Anesthesie, Beurs van Berlage	2019	0.1
Wetenschapsdag ambulancezorg	2019, 2020	0.2
Tutoring, Mentoring		
Scientific internship medical student	2017, 2018	2

3. Parameters of Esteem

Awards and Prizes	Year
Paul Dudley White International Scholar Award	2019
Best cardiac arrest presentation NAEMSP annual meeting	2020
Winner Best of the best abstracts, European Resuscitation Council (ERC) Congres	2020

About the author

Corina de Graaf was born in Bunschoten-Spakenburg, the Netherlands on January 8, 1991 to Jaap and Aleida de Graaf. She was the oldest daughter and grew up with her younger siblings Elien, Lars and Annewil. In 2009, she graduated from pre-university education (VWO, GSG Guido de Bres in Amersfoort). In the same year she applied for the study Medicine with numerus fixus but was not selected after which she started with a Bachelor of Nursing. In 2010 she tried to enroll in the study Medicine again by entering the selection procedure of the University of Amsterdam with success leading to the start of her Medicine study. During her study she moved to Amsterdam in 2012. She obtained her qualification as a medical doctor in 2016.

During the scientific internship of the Master in Medicine in 2016 under the supervision of dr. H.E. Endeman, intensivist at the time in the OLVG hospital, she came into contact with the Amsterdam Resuscitation Studies (ARREST), part of the department of Cardiology of the Academic Medical Centre in Amsterdam. After which dr. S.G. Beesems and dr. R.W. Koster became also part of the supervision of her internship project focusing on out-of-hospital cardiac arrest (OHCA) patients transported without return of spontaneous circulation (ROSC). This collaboration resulted in the start of her PhD project in 2017 under the supervision of dr. R.W. Koster, dr. S.G. Beesems, prof. dr. A.A.M. Wilde and prof. dr. J.P.S. Henriques. Her research focused on new technology developed for automated external defibrillators (AED) allowing rhythm analysis with ongoing chest compressions and the decision-making in OHCA patients without ROSC. After her PhD project of four years she started in February 2021 as a medical doctor in the internal medicine department of the UMC Utrecht.

Corina lives in Leusden, together with Laurens van Ee and his daughter Lis.

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Toen ik begon aan mijn wetenschappelijke stage naar reanimaties buiten het ziekenhuis, had ik nooit kunnen dromen dat die zou eindigen met een promotie traject en mooi proefschrift. Deze mijlpaal heb ik natuurlijk niet alleen bereikt maar met de hulp en ondersteuning van veel mensen die direct of indirect een grote steun voor mij zijn geweest. Een aantal personen wil ik in het bijzonder bedanken:

Promotor prof. dr. A.A.M. Wilde
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Promotor prof. dr. J.P.S. Henriques
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Co-promotor dr. R.W. Koster
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Co-promotor dr. S.G. Beesems
Beste Steffie, bedankt voor de rust en stabiliteit tijdens de wetenschappelijke discussies tussen Ruud en mij. Jij wist vaak op het juiste moment in te breken en de kern eruit te pakken zodat we daarna weer verder konden. Bedankt voor de steun en het vertrouwen dat dit eindresultaat er zou komen.

Leden van de promotiecommissie
Geachte leden van de promotiecommissie: prof. dr. S.A.J. Chamuleau, prof. dr. K. Monsieurs, prof. dr. P.W.B. Nanayakkara, prof. dr. R. de Vos, dr. H. Endeman, prof. dr. R.J.G. Peters. Ik dank u hartelijk voor de inhoudelijke beoordeling van mijn proefschrift en uw bereidheid hierover met mij van gedachten te wisselen tijdens de openbare verdediging.

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Lieve Iris en Laura, wat hebben wij veel uren met elkaar doorgebracht op de werkvloer maar ook daarbuiten. Ik wil jullie bedanken voor de steun, het altijd paraat staan als ik even wilde klagen als het tegen zat en natuurlijk ook voor momenten van ontspanning tijdens borrels en stapavondjes. Met als hoogtepunt ons gemeenschappelijke congres in Philadelphia.

ARREST team
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