INCIDENCE, OUTCOMES AND CHARACTERISTICS OF REARREST AFTER OUT-OF-HOSPITAL CARDIAC ARREST

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ABSTRACT

Out-of-hospital cardiac arrest (OHCA) results in nearly 350,000 deaths in the United States annually. Survival after OHCA is dismal, with regional estimates suggesting an overall case fatality rate of between 92% and 96%. High mortality following OHCA persists despite advances in resuscitation methodology that result in the successful resuscitation of a substantial fraction of patients (~40%). It is known that some patients experience another OHCA after resuscitation. This secondary OHCA, called *rearrest*, has not been extensively characterized, but it is known that rearrest correlates with poor OHCA survival prognosis after OHCA. Further understanding of rearrest may enable its prevention and development of optimal treatment strategies, potentially increasing survival after OHCA.

Utilizing data from the OHCA surveillance program of the Resuscitation Outcomes Consortium, this dissertation addresses the need for further characterization of rearrest, focusing on patient, treatment, and electrocardiographic characteristics.

The results of this study indicate several characteristics that distinguish cases with and without rearrest. Of these, median income and electrocardiographic characteristics derived from the QT-interval were the most robustly associated with rearrest case status. Time-to-rearrest was correlated with rearrest event number, presenting OHCA electrocardiogram rhythm, and when

measured over the first 5-minutes following resuscitation in patients with rearrest, standard deviation of heart rate.

While the characterization of rearrest cases was comprehensively reported with the available data in this study, limited inference could be drawn regarding the prediction and prevention of rearrest due to a lack of patient history data and a large amount of missing electrocardiographic data. Still, this study lays down a clear path to future research, indicating promising directions for further filling in the knowledge gaps necessary to increase survival after OHCA.

The public health significance of this work is rooted in the identification and characterization of an important determinant of a major source of mortality in the developed world, OHCA. The findings of this study provide a novel basis for further investigations aiming to save some of the hundreds of thousands of lives that are claimed by OHCA each year, potentially through public health interventions executed through emergency medical services.

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PREFACE

I have a running joke with my wife – Kat – that my obituary should begin, “He was eaten by sharks.” The rationale for this is that no matter what good or bad ultimately comes out of my life, nothing could overshadow the magnitude of that statement. But I guess that is a matter of perspective and semantics… The years of work that led up to this dissertation were, frankly speaking, largely spent studying the process and conditions of bringing the clinically dead back to life. Depending on where the rest of my life goes, that might make a pretty good follow up to the sharks.

Many thanks are due to my advisor, Dr. Orchard, for accepting the burden of advising me despite my extra-departmental project and my general stubbornness. Without his patience and guidance, I am certain that I would not have finished this work. I must also express a great debt of gratitude to Drs. Akira Sekikawa and Stephen Wisniewski, who graciously gave their time and effort to support my work.

Special thanks are due to my research mentor, Dr. Menegazzi, who started my career by asking, “Are you sure you want to work with dirty, smelly pigs?” and then generously shared his lab, projects and friendship.

This work could not have happened without the support of the National Institutes of Health, the National Heart, Lung and Blood Institute, the Resuscitation Outcomes Consortium, and the faculty and staff of the Departments of Emergency Medicine and Epidemiology.

Lastly, my deepest thanks go to the University of Pittsburgh, the greatest institution for research and education in the world.

1.0 INTRODUCTION

The scientific context of this thesis is that of out-of-hospital cardiac arrest (OHCA) and resuscitation, which in the developed world both exist for the most part within the larger context of chronic cardiovascular disease. OHCA claims many lives in the United States annually, and while it is treatable, it has an exceptionally high case fatality rate owing to the extremity of the conditions to which it subjects the body. The pursuit of a reduction in deaths due to OHCA, independent of prevention of the OHCA itself, is contingent upon developing optimal resuscitation methods to restart the heart and optimization of post-resuscitation care to improve long-term outcomes.

Prehospital rearrest is one potential target for interventions aiming to reduce OHCA case fatality rates. Sequentially located between successful resuscitation and admission to the hospital, rearrest is a clinical turning point that for many patients presages death. This thesis provides the most detailed characterization to date of the incidence, outcomes, and characteristics associated with rearrest in an effort to understand, predict and someday perhaps prevent it. The hope is that with this work, the foundations will be laid for future gains in survival after OHCA.

2.0 BACKGROUND

2.1 ETIOLOGY AND INCIDENCE OF OUT-OF-HOSPITAL CARDIAC ARREST

Out-of-hospital cardiac arrest (OHCA) is the specific designation given to a cardiac arrest event occurring outside of a healthcare facility, thereby differentiating it from in-hospital cardiac arrest (IHCA). The designation, seemingly arbitrary, is reflective of the nature of cardiac arrest as a disease state and the consequences of delays in administration of its principle therapies that result from its occurrence far from physicians, medications, and critical medical devices. Cardiac arrest is the complete cessation of the normal mechanical and electrical activity of the heart. Under normal conditions, the heart serves to pump blood to the lungs, where it is oxygenated, and then to pump oxygenated blood returning from the lungs to the rest of the body, including the heart muscle itself. As oxygenated blood perfuses the body's tissues, it provides substrate for aerobic metabolism, the principle source of energy production in nearly all multicellular organisms. During cardiac arrest, this activity ceases, and the entire body undergoes global ischemia. Within 5 minutes, irreversible brain damage and other organ pathology is likely, and with every passing minute the probability of long term survival diminishes.[1,2] Under these circumstances, minimizing the time to treatment is critical, but because the patient with OHCA is not in a hospital, time to treatment is non-trivial, and in fact sometimes sufficiently long as to be detrimental.

There is no single etiology of OHCA. Rather, the definition of OHCA broadly admits traumatic or medical etiologies, where the two are generally studied separately given the radically different treatment priorities of either. Treatment of traumatic OHCA is driven by the need to reverse hypovolemic shock secondary to profound exsanguination.[1] This project will only consider OHCA of medical etiology. In the realm of medical OHCA, etiologies may be of cardiac origin or an external source. Cardiac causes of OHCA include spontaneous lethal arrhythmia, myocardial infarction, heart failure, and congenital heart defects, among others. External sources include poisoning/overdose, asphyxia, and drowning.[1] Studies have suggested that the predominant etiology of OHCA in the US is myocardial infarction secondary to advanced atherosclerosis.[3]

Estimates of the incidence of OHCA have historically overlapped estimates of the more general phenomenon of sudden cardiac death (SCD), for which practical definitions vary in the literature, but most of which include the general criterion of a cardiac arrest occurring less than 1 to 24 hours after the onset of symptoms.[4] The study of OHCA in the developed world reflects the emergence of the primary cause of OHCA from the 20th century until the present day, coronary heart disease (CHD). Beginning in the early 20th century and stretching until the 1960s, mortality rates from CHD consistently climbed in the US and Western Europe.[5] This phenomenon is generally attributed to a combination of factors including the general shift in prevalence and mortality from infectious to chronic disease, population-wide changes in lifestyle and nutrition, and the ubiquity of cigarette smoking.[5] As early as the 1930s, studies of sudden death had highlighted the importance of CHD in OHCA. A study by Hamman from 1934 presented early evidence that CHD made a significant contribution to sudden death, showing that nearly 40% of sudden deaths in one geographic area could be attributed to CHD.[6] The following year, Levy classified CHD-related deaths by suddenness and by characteristics of the CHD, showing that lesion characteristics correlated with but did not always pair with angina, a critical warning sign of myocardial infarction.[7] Autopsy studies of SCD in the 1940s from various sources provided mortality estimates ranging from 30% to 79%.[8,9] In 1960, Spain published a 10-year autopsy review covering Westchester County, New York, from 1949 to 1959.[10] Among the key findings were a 91% proportion of sudden deaths (symptoms within 1 hour) among white males attributable to CHD, a 52% proportion of sudden deaths among white women attributable to CHD, and proportions of 61% and 35%, respectively, among the former and latter when death was classified as unexpected but not sudden. In 1948, the Framingham cohort study was started as a means to shed light on the risk factors and epidemiology of CHD via long-term prospective observation of a living cohort.[11] Fourteen-year follow up of the original study cohort revealed that 77% of deaths under age 65 from heart disease in that period were due to CHD. Furthermore, 52% (62/120) of those deaths were sudden, OHCA. In the 1980s, the MONICA project, an international surveillance project for CHD morbidity, mortality and risk factor assessment, was established, providing broad geographic comparisons of CHD-related mortality rates.[12] A sub-study within the MONICA project estimated the prehospital case fatality rates due to myocardial infarction in several Northern European countries, finding that between 24.3% and 41.2% of acute myocardial infarction (AMI) case fatalities in men occurred prior to hospital arrival, compared to between 17.3% and 36.8% in women.[13]

A major theme emerging from both the MONICA project and its predecessors (convincing evidence coming from the Framingham study much earlier) was that contemporary in-hospital treatments for CHD were useless to prevent sudden death, since it frequently occurred prior to hospital admission. The epidemiological literature of the time (and currently) viewed primary prevention as the best means to avoid sudden death. In parallel, the growing field of resuscitation science in the first half of the 20^{th} century presented a means of secondary prevention, effectively buying time for patients who would have been victims of sudden death.

The CHD literature on sudden death provides a constrained, though etiologically satisfying view of SCD and OHCA, however resuscitation science is not the science of resuscitating CHD patients; it is the science of resuscitating stopped hearts. For instance, CHD literature concerning AMI and/or SCD may not capture AMI that precipitates OHCA and is followed by resuscitation and patient admission to hospital. Thus the epidemiology of SCD and OHCA with respect to resuscitation outcomes must necessarily consider all causes of SCD/OHCA, first, and second specifically capture cases in which the heart stops prior to hospital admission, regardless of downstream resuscitation outcomes. To the first end, the literature is relatively new, compared to the long history of CHD SCD research. A meta-analysis by Kong et al[4] reviewed the SCD literature and noted only 6 available studies reporting a national all-cause incidence of SCD in the US from primary data, 3 of which explicitly provided estimates of OHCA. All of these studies examined cases occurring after 1979, so our understanding of US national OHCA incidence prior to that year is at best incomplete. Methodology for ascertaining OHCA differed in the 3 studies, and included National Center for Health Statistics data, death certificate analysis, and/or EMS-focused OHCA surveillance. Prior studies have suggested that passive or retrospective death certificate analysis may be substantially less accurate or more volatile, depending on case classification details, than more intensive record collection and review employed by EMS-focused programs.[14,15] This sets up a potentially interesting comparison then between the national incidence estimate offered by Zheng[16] (12/10,000 for 1989-1998), which was NCHS and death certificate based, and those of Nichol[17] (9.5/10000 for

2006-2007) and Cobb[18] (11/10,000 for 1989), which derived from EMS-focused surveillance and record review. Interestingly, Cobb demonstrated a significant decreasing trend in OHCA incidence between 1979 and 2000, and there was relatively close agreement between his study's 2000 national incidence estimate (9.1/10000 for 1999-2000) and Nichol's aforementioned estimate for a 1-year capture period starting 6 years later.

While national incidence of OHCA may provide a general snapshot of the public health burden of OHCA, it does not capture the textured variability inherent in OHCA incidence after stratification by geographic, health status, and demographic factors. For instance, incidence of SCD is higher in men than women overall and at any age.[16] Furthermore, incidence of SCD increases with increasing age, perhaps as dramatically as doubling every 10 years beginning at midlife.[19, 20] Geographically, Nichol's results from a multi-site clinical consortium show statistically significant discrepancies between rates of OHCA across 9 North American cities (7.2/10000 to 15.9/10000 for 2006-2007). Similarly, Cheung notes large variability between several Australian cities (0.13/10000 to 8.9/10000 for several sampling intervals) across several studies, although incomplete capture may be responsible for the disparity.[21] On the other hand, Herlitz[22] reports incidence estimates for 5 Northern European cities with little variation. This observation may speak to the significance of demographic and health status factors in OHCA incidence, where the implication is that these populations are relatively similar. To this end, Becker[23] and Galea[24] showed in separate studies that incidence of OHCA differs between whites and blacks/non-whites in two US cities. Moreover, both studies concluded that differences in patient health status, particularly cardiovascular risk factors, did not significantly explain these differences. In his incidence paper, Nichol posits a relationship between geographic OHCA incidence variation and variability in time to treatment of AMI, which may rapidly degenerate into cardiac arrest.

Survival from cardiac arrest is often described in terms of survival of the patient until he or she is discharged alive from the initial receiving hospital. This measure is supplemented in the clinical literature with measures of neurologic outcome, although historically this has been difficult to ascertain at the population level due to the time and resources necessary for follow-up. In the context of resuscitation, these measures are best characterized as long term outcomes, compared to outcomes more proximate to an OHCA event. Case in point, in order for a patient to survive to hospital discharge, the function of the heart must be restored, an event called return of spontaneous circulation (ROSC), which is the most immediate endpoint of all successful resuscitations. The revised Utstein template – a guideline for uniform OHCA and resuscitation research - provides the following definition of ROSC: "the restoration of a spontaneous perfusing rhythm that results in more than an occasional gasp, fleeting palpated pulse, or arterial waveform." [25, 26] This definition is implicitly duration-independent, although the template provides a vague further qualification that ROSC applies to pulsatile events "approximately [greater than] 30s."

2.2 SURVIVAL AFTER OUT-OF-HOSPITAL CARDIAC ARREST

Survival rates after cardiac arrest are unequivocally low. Nichol reports 4.4% survival overall for 2006-2007, with a range of 1.1-8.1% in 9 North American cities, for all OHCA assessed by EMS.[17] For only those cases receiving some treatment from EMS, the same study reports an overall survival rate of 7.9%, with a range of 3.0 – 16.3%. The CARES registry, a multi-site clinical surveillance network for cardiac arrest with 23 participating sites in the US, reported an overall survival rate of 9.6%, and survival with “Good” or “Moderate” neurologic outcome of 6.9%.[27] Cobb reports a survival rate of 15.1% for the period from 1999-2000 based on a sample from Seattle, WA.[18] This number is not adjusted for the US population however and tracks closely with the Seattle site estimate (16.3%) from Nichol’s study.[17] Various international studies also report survival rates ranging from 6.6-23%, although study parameters vary. [22, 28-30]

There are several known factors that have been associated with survival after OHCA. Women tend to survive OHCA more often than men,[31] and the mean age of survivors tends to be less than that of non-survivors.[32] Additionally, at least two studies suggest that some categories of increased body mass index (BMI) result in higher rates of survival or improved neurologic outcome relative to lower and more obese categories.[33, 34] The most prominent non-demographic factor is perhaps the presenting or “first EMS assessed” electrocardiogram (ECG) rhythm of the OHCA event. When considering only patients with an initial EMS-assessed cardiac rhythm of ventricular fibrillation (VF), overall survival in Nichol’s study increased to 21%, with a range of 7.7-39.9%.[17] Similarly, Cobb found survival to be as high as 32% for patients with a first OHCA rhythm of VF.[18] This compares to 2.2% for patients with asystole and 4.9% for patients with pulseless electrical activity (PEA). First assessed ECG rhythm connects directly with one of the two primary therapies for cardiac arrest, defibrillation. In theory, patients presenting with VF can have a shorter global ischemic insult prior to successful defibrillation (i.e. ROSC), thereby limiting the effects of ischemia on the vital organs.[1,2] A related factor affecting survival is location of OHCA. Patients experiencing OHCA in public places have a greater probability of surviving to hospital discharge, perhaps due to proximity to CPR providers and defibrillators.[35] Likewise patients with OHCA that is witnessed by EMS, thus prompting expeditious treatment, are more likely to survive.[36]

Lastly, survival after OHCA is to an extent a function of race and economic status. Galea[15] found that blacks were less than half as likely than whites to survive to hospital discharge following OHCA, a result that was mirrored by Becker's[23] study. At least one study showed a correlation between one measure of socioeconomic status (SES) and survival, where lower SES was associated with poorer outcomes.[37]

Survival is dependent upon though not guaranteed by ROSC, so estimates of survival do not give a full picture of what proportion of patients do regain pulses during the course of treatment. However, several direct estimates of the incidence of ROSC are available in the literature. The CARES group for instance reports a rate of 34% ROSC prior to arrival in the emergency department.[27] This compares to an estimate of 28% reported by Nichol[17] and 35% reported by Cobb.[18] The ascertainment of ROSC historically has had less obvious utility at the population level than ascertainment of survival to hospital discharge, in part because until 2002 and the advent of post-cardiac arrest therapeutic hypothermia, in-hospital post-arrest care was largely limited to life support.[38, 39] That is to say, ROSC is a moot point if the prognosis after ROSC is as poor as it generally is for OHCA, as evinced by survival rates. Still, ROSC is commonly an endpoint in clinical trials of resuscitation therapies.

2.3 REARREST AFTER RESUSCITATION FROM OUT-OF-HOSPITAL CARDIAC ARREST

Resuscitation does not necessarily correct the underlying pathology that leads to a cardiac arrest event. Take for example the case of coronary arterial occlusion leading to AMI, in turn precipitating VF. Successful defibrillation of the heart in this case simply reestablishes electro-mechanical synchrony and cardiac output; further intervention, e.g. coronary artery bypass grafting or coronary stent placement, is necessary to correct the primary cause of the cardiac arrest. These downstream corrective therapies are currently impossible outside of the hospital; therefore the resuscitated OHCA patient is at risk of cardiac arrest due to the same cause immediately after ROSC is attained. The recurrence of cardiac arrest following successful ROSC is a phenomenon known as rearrest. The direct study of rearrest as a general phenomenon is relatively new, however the loss of pulses subsequent to resuscitation has been studied in a very specific electrophysiologic context, broad temporal frame, or as a secondary endpoint in OHCA studies for decades. In contrast, the scope of the present study while limited to the prehospital environment, is generalized to all cardiac arrest rhythms, with the aim of improving care of patients following resuscitation while they are in the care of paramedics or field physicians prior to hospital admission.

The term “rearrest” is preceded in the literature by the terms “refibrillation” and “recurrent ventricular fibrillation” (hereafter used synonymously), both of which allude to the electrophysiologic manifestation of the rearrest event. While VF is only one of several ECG presentations of cardiac arrest, refibrillation has been of particular interest in the prehospital environment due to its amenability to defibrillation and the known relationship between prompt resolution of cardiac arrest and long term outcomes (discussed earlier). However, because ascertainment of refibrillation does not capture all possible cardiac arrest rhythms, estimates of rearrest derived from refibrillation studies may theoretically under-report rates of rearrest. On the other hand, studies that ascertain only refibrillation but follow patients beyond hospital admission may theoretically over-estimate rearrest events relevant to paramedics. Bearing these limitations in mind, several estimates of prehospital refibrillation rates are available in the literature, though the applicability of each estimate is a function of the context in which it was made. (A table of many of the rearrest studies discussed in this review is provided at the end of this document.)

In one of the earliest studies incorporating out-of-hospital treatment, a 1981 North Ireland study of 141 patients reported a rate of recurrent ventricular fibrillation of 41% after OHCA[40]. The authors used a definition of recurrent ventricular fibrillation that essentially excluded prehospital rearrest events, defining a rearrest event as occurring 40 minutes or greater following successful defibrillation. This compares to a 1982 study that found a 67% rate of refibrillation prior to hospital admission.[41] Both studies were conducted prior to the adoption of the modern biphasic defibrillation waveform, perhaps limiting generalization to current practice. A 2001 paper reporting the results of a sub-analysis of the Optimal Response to Cardiac Arrest (ORCA) study in Northern Europe, reported refibrillation rates of 72-81%, although there is little detail in the paper specifying the definitions or ascertainment constraints for refibrillation.[42] Interestingly, relating to the previous paper, Martens found no statistically significant difference in refibrillation between patients treated with monophasic or modern impedance-compensating biphasic defibrillators. In a 2002 study, White and Russell reported a refibrillation rate of 61%, but also provided further texture indicating that 35% of those patients who did refibrillate, did so more than once.[43] Moreover, in the same study, the authors found no relationship between refibrillation and the outcomes of survival to hospital discharge or neurologically intact survival. A 2003 study in Amsterdam found a 79% rate of refibrillation, but also found that the median time from successful shock to refibrillation was somewhere between 45 and 52 seconds, depending on the shock number.[44] Interestingly, van Alem found that increasing number of refibrillation events was inversely correlated with survival to hospital discharge, and that refibrillation often went untreated for longer than a minute. In a 2004 study considering intervals when patients were treated only by police first responders or firefighters after suffering a witnessed VF-rhythm OHCA, Hess and White reported a 52% rate of refibrillation and no association with survival to hospital discharge.[45] The study furthermore found no association between refibrillation and bystander-delivered cardiopulmonary resuscitation (CPR). In 2008, Koster reported a similar study considering patients presenting with VF-rhythm OHCA, but not necessarily witnessed, and observed a refibrillation rate of 74% overall and 48% up to 2 minutes following first ROSC.[46] In the same study, Koster observed a significant decrease in cardiac response to shocks after the first refibrillation, suggesting that correction of refibrillation may not be as simple as delivering another shock. Further results offset this finding somewhat, however, indicating that stability of post-shock normal sinus rhythm actually increased after multiple recurrences. Finally, in a 2010 study, Berdowski (working with Koster) found rates of refibrillation between 76% and 81%, depending on resuscitation guidelines used (AHA 2000 vs AHA 2005) by EMTs.[47] In a separate study, the same author found a significant inverse relationship between time spent in refibrillation and neurologically intact survival.[48]

The preceding studies only considered rearrest events with VF ECG rhythms, and the vast majority considered only cases with initial cardiac arrest rhythms of VF. When considering rearrest of all presenting rhythms, and of all initial arrest rhythms, the available literature dramatically shrinks. A 2010 Pittsburgh-based study by Salcido ascertained rearrest in all initial and rearrest rhythms treated by any level of EMS, finding a rearrest rate of 36% and a lower but not significantly different rate of survival to hospital discharge in cases with rearrest compared to those without.[49] The same study reported the proportions of rearrest rhythms, finding that the most prevalent rearrest rhythm, contrary to the focus of historical rearrest literature, was pulseless electrical activity, a periodic electrical rhythm with no accompanying mechanical cardiac activity. Lastly, the same study also reported a median overall time from ROSC to rearrest of 3.1 minutes and 3.8 minutes for first ROSC to first rearrest. Also in 2010 and also in Pittsburgh, Hartke reported a highly specialized rate of rearrest of only 6%, ascertained in helicopter transported cardiac arrest patients.[50] While the study was indeed conducted in the prehospital theater and admitted all rearrest rhythms, helicopter EMS services utilize different treatment strategies and often select patients based on severity, making this study non-comparable to studies examining rearrest treated by ground units. More comparably, a 2011 study by Lerner in Milwaukee, also admitting all initial and rearrest rhythms, found a 39% rate of rearrest, but unlike the Pittsburgh study did find an inverse association between rearrest and survival to hospital discharge.[51] Lerner furthermore found that the location of rearrest - at the scene or en route to hospital - did not have a significant effect on survival. Finally, in 2012 Chestnut reported a generalized rearrest rate of 5% in a small, Birmingham, Alabama study.[52] Chestnut reported rearrest under an umbrella term, cardiovascular collapses (CVC), intended to capture the general loss of life-sustaining vital function. However, the only patients that qualified in this study for CVC were patients who had clearly undergone rearrest.

Consensus in the literature indicates with little evidence that the most likely cause of rearrest is the same underlying pathology that led to the primary cardiac arrest event. However, the dynamics of the resuscitation process leave open many avenues of detriment for the patient, with plausible bases for increasing the likelihood of rearrest. Consider that the post-arrest patient may be dependent on prehospital care providers for ventilation, pressure management, antiarrhythmic administration, and other life support measures. Consider also that misapplication of therapies in the same context could occur to the detriment of an unstable patient. Research in the realm of refibrillation has identified some possible contributors to rearrest, including chest compressions and antiarrhythmic administration.

In 2005, Hess and White conducted a study responding to an abstract-only report[53] indicating an association between chest compressions following successful shocks and refibrillation, finding in contradiction to the abstract that refibrillation occurs more often in the absence of post-shock chest compressions than in their presence.[54] Orsorio, however, reported in 2008 an animal study outlining a mechanism and evidence for electro-mechanical induction of refibrillation when chest compressions were synchronized with critical ECG structures.[55] Chronologically, Berdowski's aforementioned 2010 study would later show that resumption of CPR following successful defibrillation was significantly associated with refibrillation.[47] Berdowski's study included groups with "immediate" (allowing some minimal procedural delay) and intentionally delayed post-shock continuation of CPR, but no group without post-shock CPR. Even so, the hazard of refibrillation was dramatically higher after the initiation of CPR in both groups than in the time between the shock and start of CPR.

The role of antiarrhythmics in preventing rearrest has been considered directly and indirectly. However, there is little evidence for the application of antiarrhythmics either for resuscitation or for preventing rearrest. Current AHA resuscitation guidelines indicate the antiarrhythmics amiodarone and lidocaine may be used to treat "VF or pulseless VT unresponsive to CPR, defibrillation, and a vasopressor therapy."[56] A 1999 study by Kudenchuk found that amiodarone administered to patients after 3 failed defibrillation attempts significantly increased survival to hospital admission when compared to placebo, which might be interpreted as a reduction in risk of rearrest due to lethal arrhythmia.[57] Dorian published results of a similar study in 2002 comparing amiodarone to lidocaine with no placebo-only group in patients with 4 failed shocks and epinephrine administration.[58] This study found that amiodarone increased rates of survival to hospital admission relative to lidocaine (OR: 2.17) and that this effect was consistent whether amiodarone was given early or late, defined by delivery prior to or subsequent to the median dispatch to drug delivery interval of 24 minutes.

3.0 SPECIFIC AIMS

The literature reveals a clear deficiency in research concerning rearrest, its characteristics, and its effects. Following on the investigational path of an associated but non-qualified[*] precursor study that established the incidence of rearrest and its relationship to survival (Appendix A), the proposed study will use data acquired from the Resuscitation Outcomes Consortium to investigate the following aims.

Aim 1: Describe and compare the patient and resuscitation treatment characteristics of cases with and without rearrest.

Aim 2: Describe and compare the electrocardiographic characteristics of cases with and without rearrest.

Aim 3: Create a predictive model for anticipating impending rearrest.

* - Appendix A was originally proposed as a central and essential component of this doctoral research project, but was completed by the author prior to official consent of the committee and so could not be evaluated as originally intended.

4.0 CASE CHARACTERISTICS OF REARREST AFTER OUT-OF-HOSPITAL CARDIAC ARREST

To be submitted for publication

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4.1 ABSTRACT

BACKGROUND/AIMS: Rearrest (RA) is the condition wherein a patient who successfully achieves return of spontaneous circulation (ROSC) from out-of-hospital cardiac arrest (OHCA) experiences another cardiac arrest prior to arrival at the hospital. A previous study demonstrated an inverse association between RA and survival in OHCA patients. The current study was conducted to explore how patient, temporal, and treatment factors may be associated with RA.

METHODS: Prehospital data were obtained for emergency medical services -treated, non-traumatic OHCA with prehospital ROSC, and incident dates ranging from 2006 to 2008, from the Resuscitation Outcomes Consortium (ROC), a multi-site clinical research network conducting population level surveillance of OHCA in 11 cities in the US and Canada. RA case status for each case was established in a previous study, and characteristics were compared between cases with and without RA in 3 categories: patient/setting, time-to-event intervals, and interventions/drugs. Means were compared with t-tests, and proportions were compared with the χ^2 test. Multiple logistic regression was used to assess the relationship between selected characteristics and RA in general, and again in a separate model considering only characteristics that could be definitively localized to the period prior to RA.

RESULTS: A total of 3,251 OHCA cases with ROSC were included in this study. Of these, 568 (17.5%) had at least one RA. In a general analysis, RA was inversely associated with first rhythm ventricular fibrillation / ventricular tachycardia and time to ROSC, and directly associated with median income, time to transport, defibrillation, and atropine administration. In a analysis restricted to only pre-RA characteristics, only median income was related to RA. **CONCLUSIONS:** Several case characteristics were found to be associated with RA, however the cause and effect relationship with all such characteristics remains uncertain.

4.2 INTRODUCTION

Rearrest (RA) is the condition wherein a patient successfully resuscitated from out-of-hospital cardiac arrest (OHCA) experiences another cardiac arrest prior to arrival at the hospital. RA may manifest in ventricular fibrillation / ventricular tachycardia (VF/VT), pulseless electrical activity (PEA), or asystole on the electrocardiogram (ECG), and necessarily encompasses within its scope the terms refibrillation and recurrent ventricular fibrillation. The scientific literature regarding RA is largely limited to the subcategory of RA manifesting as refibrillation or recurrent ventricular fibrillation.[41-46] However, a handful of studies have provided estimates of the incidence and outcomes of RA in limited geographic areas.[48-52]

In a previous study (presented in Appendix I), results were presented of a multi-site analysis of rates of RA after out-of-hospital OHCA, as well as the relationship between RA and survival to hospital discharge.[59] The results of that study showed that RA has a strong inverse relationship to patient survival following OHCA, indicating that RA is a significant clinical phenomenon in the treatment of OHCA, not simply an innocuous temporary state. Despite this finding, many questions were left unanswered; more work is necessary in order to understand who RA affects, how it should be treated, and whether it can be prevented.

In the present study, the patient and clinical characteristics of the cohort from the aforementioned study were considered. The aim was to provide both a comprehensive description of the characteristics of cases with RA, for which there is no analog to date in the RA literature, as well as to investigate associations between these characteristics and occurrence of RA. Toward this end, additional emphasis was placed on characteristics that could potentially be temporally ascertained prior to a RA event, providing some delineation between the causes and the effects of RA. It was hypothesized that some characteristics could prove helpful in predicting RA, although no a priori judgments were made as to which characteristics these would be.

4.3 METHODS

The University of Pittsburgh Institutional Review Board approved this retrospective study. Case data for emergency medical services (EMS)-treated OHCA patients were obtained from the Resuscitation Outcomes Consortium (ROC), a multi-site clinical research consortium investigating OHCA and severe trauma in 11 cities in the United States and Canada. Cases included in this study were originally collected from the period spanning January 2006 to December 2008, through the population-level OHCA surveillance operations of the ROC in 10 of the 11 participating cities, in cooperation with local emergency medical services (EMS) agencies. Case data included patient demographics, treatments, critical event times, and patient outcomes, derived from computer assisted dispatch (CAD), EMS prehospital patient care reports (PCRs), electronic defibrillator downloads, and hospital records. All data elements were abstracted from records at the local ROC sites and aggregated electronically at the data coordinating center (DCC) at the University of Washington. The DCC then provided a single de-identified database, as well as any available defibrillator download files containing ECG and cardiopulmonary resuscitation (CPR) process signals (transthoracic impedance, continuous compression depth and force) for patients who achieved return of spontaneous circulation (ROSC) prior to hospital arrival.

All cases in the initial study cohort were analyzed for evidence of RA. The three-fold approach to identifying RA employed here has been previously described elsewhere, but is briefly described herein. RA was ascertained through a combination of Direct Signal Analysis (Method 1) – by which defibrillator download files were examined for ROSC followed by lethal arrhythmia and resumption of resuscitation efforts -, Indirect Signal Analysis (Method 2) – by which the minute-by-minute CPR process measurements of cases without currently available signals were analyzed for evidence of ROSC followed by further CPR -, and emergency department (ED) vital status assessment (Method 3)– by which patients who had some prehospital ROSC but arrived pulseless at the ED could be inferred to have had at least one RA. The combination of these 3 methods of RA ascertainment, giving status identification priority first to Method 1, then Method 2, and finally Method 3, resulted in single RA status indicator.

Three general categories of patient and clinical data were available for characterization of the study cohort. The categories comprised Patient/Setting, Drugs/Interventions, and Time Intervals. A summary of characteristics in each category is provided below.

Patient / Setting Characteristics included limited demographic information about the patient (age, sex, white race), as well as community-level demographic information (percentage adults > 25 years old without a high school diploma, unemployment rate, and median household income) pertaining to the census tract in which the OHCA occurred derived from year 2000 US Census data. Included in this category was also the general sub-category of contributing non-cardiac causes of the primary OHCA. ROC data collection forms provided for 21 unique non-cardiac causes, 14 of which (Anaphylaxis, Chemical Poisoning, Drowning, Drug Poisoning, Electrocution, Foreign Body Obstruction, Hanging, Mechanical Suffocation, Non-Traumatic Exsanguination, Respiratory Condition, Smoke Inhalation, Strangulation, Terminal Illness, and Other Obvious Cause) were represented in the cohort. These categories were collapsed into a signal non-cardiac contributing cause variable for the purpose purpose of analysis. Lastly, variables were also included that captured detail about the immediate setting in which the OHCA occurred (Bystander Witnessed, EMS Witnessed, Public Location) and the proportion of patients in a shockable ECG rhythm, i.e., ventricular fibrillation / ventricular tachycardia (VF/VT), upon first EMS rhythm assessment.

Interventions included the most common cardiac arrest therapies – CPR and defibrillation -, ECG monitoring, advanced airway placement, intravenous/intraosseous (IV/IO) line placement, end-tidal CO_2 monitoring, and transthoracic pacing. Drugs included epinephrine, sodium bicarbonate, atropine, amiodarone, and lidocaine. Capture for interventions and drugs was limited to "ever given" versus "not given", and administration could not definitively be localized to the period before, during, or after RA if present. However, total dose of epinephrine in units of milligrams was available a proportion of cases.

A subset of cases in the study cohort had available CPR process measurements, including chest compression rate (CCR) and chest compression fraction (CCF), available for the first 20 minutes of EMS CPR. Case average, minimum and maximum of these process measures were calculated from the non-zero measures available for each case. Additionally, case average CCR was transformed as a dichotomous variable, reflecting compliance with the recommended guidelines for CCR (100 compressions per minute), allowing for 10% under- or over-shoot from the guideline, and compared between cases with and without RA.

Event clock times derived from CAD records, defibrillator download time markers, and PCRs, including times of 911 call received, first vehicle dispatch, first vehicle arrival (BLS or ALS), first EMS CPR, first ROSC, first shock, ground transport from scene, and arrival at ED, were routinely recorded on ROC OHCA surveillance data forms. Time intervals considered in the present study were calculated using the first available event time for each case as the start time and each of the subsequent available event times as the end of each interval. The difference between the 2 times in whole number minutes was taken as the duration of each time interval. Not all time intervals were always present; specifically time-to-first shock was only present in those cases that were defibrillated. Therefore summary statistics for this interval reflect only those cases that were shocked.

A subset of cases had signals available for Direct Signal Analysis, as described in the RA ascertainment methodology. Within this subset many cases had both CPR and defibrillation, enabling the calculation of shock pause intervals, the time intervals spanning the gaps between chest compressions necessary to deliver a defibrillating shock. These intervals included the pre-shock pause (PreSP), the post-shock pause (PostSP), and the PSP (Peri-Shock Pause). The PreSP was calculated as the time interval from the last pre-shock chest compression to the delivery of the subsequent rescue shock. The PostSP was calculated as the time interval from the rescue shock to the next chest compression. In the event of ROSC resulting from a rescue shock, there was by definition no PostSP, and the PSP and PreSP were considered equal. Otherwise, the PSP was equal to the sum of the PreSP and the PostSP for each shock.

Means and standard deviations (SD) were reported for continuous, normally distributed characteristics; medians and interquartile ranges (IQR) were reported for non-normally distributed continuous characteristics. Proportions were reported with 95% confidence intervals. Characteristics in each of the three general categories were compared between cases (RA+) and controls (RA-). Means were compared with two-tailed t-tests. Proportions were compared using the χ^2 test. Shock pause intervals were specifically compared using the Kruskal-Wallis test due to non-normally distributed values.

An initial multivariable logistic regression model was constructed to investigate the independent associations of characteristics with RA. Candidate variables for the model were selected from those characteristics that differed significantly between cases with and without RA in simple 2-group comparisons. Some candidate predictors were eliminated due to colinearity, temporal overlap, or large proportions of missing data. A backwards stepwise model building approach with an exit threshold of $p = 0.3$ was used to construct the final model. Age, sex, public location, EMS witnessed status, non-cardiac contributing cause, method of RA ascertainment (Indirect Signal Analysis & Direct Signal Analysis indicator variables with ED Vital Status method as referent), and initial OHCA ECG rhythm were locked into the model.

An additional multivariable logistic regression model was constructed in order to independently assess the association between certain characteristics determined to be plausibly temporally antecedent to a primary RA event. These included characteristics that could be assumed to remain unchanged following initial ROSC, thus contributing to the condition of the patient as the period of vulnerability to RA ensued. These characteristics included: patient demographics, public location, EMS witnessed status, non-cardiac contributing cause, method of RA ascertainment (as in Model #1), initial OHCA ECG rhythm, time to first EMS-delivered

CPR, and time to first ROSC. The relatively small number of predictors meeting the qualification for this model permitted the inclusion of all available predictors.

All statistical tests were conducted with an alpha level of 0.05 in Stata 12 (StataCorp, College Station, TX).

4.4 RESULTS

A total of 3,251 OHCA subjects with RA ascertainment data were available for this study. Of these, 568 cases (17.5%) were classified as cases with RA and 2,685 (82.5%) were classified as controls without RA. See Figure 1 for a cohort diagram. Of the 3,251 cases ascertainable for RA, case status determination was made by Method 1 in 9%, Method 2 in 29%, and Method 3 in 62%, again reflecting differential availability of ascertainment variables.

Patient and setting characteristics, overall and stratified by RA case status, are shown in Table 1. Age, sex and white race were similar between cases and controls. Cases and controls likewise did not differ by location of primary OHCA, presenting cardiac arrest ECG rhythm, or bystander witness status. However, a higher proportion of RA cases featured an EMS-witnessed primary OHCA event and occurred in areas with significantly higher average median income than controls. Other community factors did not differ between cases and controls.

Fourteen non-cardiac causes of the primary OHCA were reported in a total of 391 (8.9%) cases in this cohort. Among those cases, unspecified other cause (30.2%), drug poisoning (22.3%), hanging (10.0%), mechanical airway obstruction (9.5%), respiratory disease (5.4%), suffocation (5.4%) and drowning (5.4%) made up the vast majority of these reported causes.

Cases without RA were more likely to have a reported non-cardiac contributing cause than those with RA (8.7% versus 5.1%; $p = 0.004$).

EMS time intervals, overall and stratified by RA case status, are shown in Table 2. Time to First Vehicle Arrival and time to First Advanced Life Support (ALS) Arrival did not differ between RA cases and controls. However, all other EMS time intervals differed significantly between groups. Mean differences of between 0.8 minutes and 3.8 minutes were observed between cases and controls, with RA cases generally having longer intervals.

Drug and intervention prevalence among cases, controls, and overall are shown in Table 3. In general, cases with RA were more likely to have CPR (i.e., not treated by defibrillation only), a defibrillating shock and transthoracic pacing than no RA controls, although IV/IO lines were more common in controls. Epinephrine, atropine, and amiodarone were significantly more common in cases with RA. The mean (SD) dose of epinephrine in cases that received some epinephrine was 4.5mg (2.7) for those with RA compared to 2.9mg (2.1) in those without RA.

Maximum CCR ($p < 0.001$) and fraction ($p = 0.02$), as well as average CCR ($p = 0.03$), were higher in RA cases than controls. Maximum PreSP ($p < 0.001$) and maximum PSP ($p < 0.001$), but not maximum PostSP ($p = 0.41$), differed significantly between cases and controls. Comparing compliance of CCR with recommended guidelines as a case average, only 36.2% (95% CI: 33.5% - 38.9%) of cases exhibited CCR compliance overall, and CCR guideline compliance did not differ between cases with and without RA ($p = 0.09$).

Results of the first multiple logistic regression analysis are shown in Table 4. The final model included 17 predictors, 8 of which were significantly associated with RA. Among these were time to ROSC and initial OHCA ECG rhythm, which were inversely related to RA, and public location, median household income, time to transport from the scene, defibrillation by

EMS, and atropine administration, which were directly related to RA. Both ascertainment sources in the model were significantly associated with RA relative to the ED Vital Status ascertainment method, Indirect Signal Analysis being inversely related to RA (OR: 0.59; 95%CI: 0.45 – 0.76) and Direct Signal Analysis being directly related to RA (OR: 2.78; 95%CI: 2.09 – 3.70).

Results of the causally-focused multivariable logistic regression analysis are shown in Table 5. Median income quartile was directly related (OR: 1.15; 95%CI: 1.04 – 1.28) to RA. Both ascertainment sources in the model were once again significantly associated with RA relative to the ED Vital Status method.

4.5 DISCUSSION

This study provides a preliminary characterization of cases with RA and a detailed compared to cases without RA. Simple unadjusted comparisons revealed many differences between cases based on RA status in each of 3 arbitrary but conceptually useful categories of patient and clinical characteristics measured before, during and after prehospital ROSC. Multivariable logistic regression models hinted at characteristics that could be independently associated with RA, however these left open the question of association and causation.

Initial rhythm VF/VT was inversely related to RA in the general model. This finding differs from previous studies that found no relationship between RA incidence and initial rhythm. [49,51] The observed association disappeared in the causal model, a model that did not include defibrillation as a covariate due to the inability to localize all defibrillation events to the period prior to RA. It is important to remember that not all patients presenting with VF/VT will go on to be defibrillated, and some patients who present in non-VF/VT rhythms will go on to be defibrillated, in both cases because ECG rhythms may change throughout the course of resuscitation. Even so, one would expect VF/VT and defibrillation to correlate strongly with each other and with a downstream outcome. The association between defibrillation and RA would be expected to be explained largely by initial rhythm VF/VT, however, and in a model including both VF/VT and defibrillation, the observed effect of defibrillation might be the residual association between the simple presence of RA and defibrillation. Independently of defibrillation, VF/VT might perhaps be purely a surrogate for survival, which in turn correlates strongly with RA. In the present study, RA status designation relied upon a relatively complex ascertainment scheme, which in turn depended partly on a relatively extreme version of RA, ascertained by vital status upon ED arrival. It is likely that VF/VT initial rhythm and vital status at ED arrival are correlated, given the known survival advantage of VF/VT initial rhythm. Therefore, the inverse association between RA and VF/VT observed here could be driven by the direct relationship between VF/VT and good outcomes. In the causal model, this relationship may be obscured without adjustment for the effect of defibrillation.

Median income quartile was also directly related to RA in both the general and causal model. In previous studies, socioeconomic status has been shown to correlate inversely with OHCA incidence and survival. [37,60-61] The availability of bystander CPR, automated external defibrillators (AED), and differences in patient health status have been implicated in this phenomenon. Intuitively, one might expect the same relationship between socioeconomic status measures and RA, however the opposite relationship was observed. This finding could speak to differences in underlying pathology correlated with income, but without patient medical histories. Specific pathology aside, it may be that median income correlates with progression of pathology due to differential access to medical care. On the other hand, income may also ultimately correlate with unmeasured procedural aspects of the patient care process that might also result in differential incidence of RA. For texture, Figure 2 shows median income stratified by public/private location, though it should be noted that the effect of median income was observed independently of location. Figure 3 shows the rearrest rate by site plotted against site average median income; no clear relationship *at the site-level* is obvious between rearrest rate and median income. Finally, Figure 4 shows rearrest rate stratified by an expanded location classification variable for added texture. Categories included specific sub-categories of public and private settings, including occupationally relevant settings and recreational facilities.

Atropine was also directly associated with RA in the general model, even when adjusting for initial ECG rhythm with which it would be expected to correlate. Ostensibly this finding makes intuitive sense given advanced cardiac life support (ACLS) guidelines that recommend administration during prolonged resuscitation, bearing in mind that RA necessitates additional resuscitation efforts. Despite the congruence of this finding with guidelines, one cannot rule out an as yet unidentified relationship between atropine and RA, particularly as the data for this study was limited to "ever given" for drugs. In practice, paramedics may administer atropine in response to repeated bradychardic or asystolic events[62], whether it was RA events presenting as asystole or slow PEA that specifically results in the observed relationship between RA and atropine remains to be seen. At the same time, defibrillation by EMS was directly related to RA even while controlling for initial OHCA ECG rhythm. While it is intuitive that RA presents a potential opportunity for defibrillation even in a case that initially presented as a non-shockable rhythm, it is unclear at this time if this is the origin of the observed association.

It was also shown in separate analyses that process parameters of CPR differed between patients with and without RA. Surprisingly, maximum chest compression rate and maximum chest compression fraction were higher in patients with RA, although the difference in mean rates/fractions between cases and controls may have little clinical significance. Recent papers have suggested that higher chest compression rates and fractions may be better for survival,[63-64] and there is no obvious mechanism for faster chest compression rates leading to RA in particular. Investigating shock pause intervals, it was found that patients with longer maximum PreSPs and PostSPs tended to be more likely to experience RA. This result is consistent at the very least with previous studies suggesting the detrimental effect of longer shock pause intervals on survival,[65-67] now extended to a potential avenue for that effect: increased incidence of RA. While it is tempting to interpret this relationship as causal, it may also be the case that longer shock pause intervals correlate procedurally with RA, not just physiologically. For instance, when a patient experiences RA, the PreSP is derived from the start of the lethal arrhythmia to the shock. This interval may inherently be longer than PreSPs occurring during on-going CPR since the duration of the interval is not dependent upon the expedience with which the provider detects the need for a shock.

This study has a number of limitations that constrain applicability and inference. First, as described in a previous study, a mixed RA ascertainment methodology was used that produced a conservative estimate of RA. The result may be an inherent bias toward the null when it comes to differentiating cases with RA from controls. Second, all of the characteristics in this study reflect whole-case or time-independent aggregate measures. That is, this study largely lacks the resolution to determine whether interventions or drugs were administered prior to ROSC, RA, or specific individual interventions. Third, in this study ECG characteristics were not considered beyond presenting OHCA ECG rhythm because a proper comprehensive exploration of ECG characteristics and their relationship to RA deserves a dedicated analysis that would step out side the scope and purpose of this paper. Fourth, while this study includes patients from a broad geographic area, the patient populations whence the cases data were drawn may not permit generalization to all patients everywhere, particularly those with limited access to major urban hospitals, uniform and timely emergency care, or western lifestyles and health patterns. Finally, the subjects included in this study were accrued from a relatively narrow time period that predated the 2010 AHA Guidelines. Time and changing resuscitation protocols may limit generalization of these findings to current patients.

4.6 CONCLUSIONS

In a general model open to all potential case characteristics, at least one characteristic from each of 3 general categories was associated with RA. In a model restricted to characteristics that could be definitively measured prior to RA occurrence, only median income was associated with RA incidence.

4.7 TABLES

Table 1. Patient and Setting Characteristics Stratified by Rearrest Status

Characteristic	Overall	RA (-)	RA (+)	p
Patient:	---	---	---	---
Age, y	63.8(17.0)	63.6(16.9)	64.6(17.3)	0.22
Male, %	63.6(61.9-65.3)	63.3(61.5-65.2)	64.8(60.8-68.7)	0.52
Unknown Race, %	73.1 (71.8-74.4)	72.5 (70.8-74.2)	77.6 (74.2-81.1)	0.01
Public Location, %	21.9(20.5-23.3)	21.7(20.2-23.3)	22.7(19.3-26.2)	0.61
Bystander Witnessed, %	62.8(61.0-64.7)	63.2(61.2-65.2)	60.9(56.4-65.3)	0.34
EMS Witnessed, %	12.6(11.5-13.8)	12.0(10.7-13.2)	15.7(12.7-18.7)	0.02
Presenting OHCA ECG Rhx VF/VT, %	42.9(41.1-44.6)	44.2 (42.3-46.2)	44.6 (40.5-48.8)	0.85
Non-Cardiac Contributing Cause	8.7 (7.7 – 9.8)	5.1 (1.5 – 5.7)	8.1 (7.2 – 9.0)	0.004
Community	---	---	---	---
Over 25yr Old with No High School Diploma, %	16.4(16.0-16.7)	16.5(16.1-16.9)	15.9(15.1-16.6)	0.16
Unemployment Rate, %	6.5(6.3-6.6)	6.5(6.3-6.7)	6.4(6.0-6.8)	0.53
Median Household Income, $US	52856.8(21344)	52486.6(21325)	54620.3(21366)	0.04

Note: Age and Median Household Income reported as mean (standard deviation). All others reported as % (95% confidence interval).

Abbreviations: OHCA – ECG – Electrocardiogram; Out-of-Hospital Cardiac Arrest; RA – Rearrest; Rhx – Rhythm; VFVT – Ventricular Fibrillation / Tachycardia; $US – United States Dollars

Table 2. Time-to-Event Intervals Stratified by Rearrest Status

Time Interval	Overall, Mean(SD)	RA (-), Mean(SD)	RA (+), Mean(SD)	p
First Vehicle Arrival, minutes	5.8(4.3)	5.8(4.6)	6.0(3.0)	0.21
First ALS Arrival, minutes	9.3(6.8)	9.2(6.9)	9.6(6.4)	0.25
First EMS CPR, minutes	9.6(7.8)	9.5(7.7)	10.3(7.9)	0.04
First Shock Assessment, minutes	11.4(8.0)	11.3(8.0)	12.0(7.9)	0.097
First Shock, minutes	14.2(10.1)	13.5(9.3)	16.6(12.5)	<0.001
First ROSC, minutes	24.2(12.6)	23.9(13.0)	25.7(10.8)	0.003
Transported from Scene, minutes	36.2(13.1)	35.7(13.0)	38.8(13.1)	<0.001
Arrival at Emergency Department, minutes	44.7(15.4)	44.0(15.3)	47.6(15.4)	<0.001

Abbreviations: ALS – Advanced Life Support, CPR – Cardiopulmonary Resuscitation, ROSC – Return of Spontaneous Circulation, RA – Rearrest, SD – Standard Deviation.

Table 3. Interventions and Drugs Stratified by Rearrest Status

Characteristic	Overall %,(95%CI)	RA (-) %,(95%CI)	RA (+) %,(95%CI)	p
Intervention	------	------	------	------
CPR	98.3(97.9-98.7)	98.0(97.5-98.5)	99.6(99.2-100.1)	<0.01
Advanced Airway	88.4(87.3-89.5)	88.1(86.8-89.3)	90.0(87.5-92.5)	0.19
Intravenous/Intraosseous Line	16.2(14.9-17.5)	17.3(15.9-18.8)	10.9(8.4-13.5)	<0.001
Defibrillating Shock	54.2(52.5-55.9)	52.5(50.6-54.4)	62.3(58.3-66.2)	<0.001
End Tidal CO_2 Monitoring	58.8(57.1-60.4)	58.5(56.6-60.3)	60.0(56.0-64.1)	0.49
Transthoracic Pacing	6.0(5.2-6.8)	5.3(4.4-6.1)	9.5(7.1-11.9)	<0.001
Drug	------	------	------	------
Epinephrine	77.2(75.7-78.6)	75.1(73.4-76.8)	86.7(83.9-89.5)	<0.001
Bicarbonate	21.7(20.2-23.2)	21.0(19.4-22.7)	24.8(21.1-28.4)	0.06
Atropine	59.8(58.1-61.6)	56.7(54.8-58.7)	74.1(70.4-77.8)	<0.001
Amiodarone	7.5(6.5-8.5)	6.8(5.8-7.8)	10.5(7.8-13.1)	<0.005
Lidocaine	6.0(5.2-6.8)	27.1(25.3-28.8)	31.0(27.1-34.9)	0.06

Note: All treatments/drugs are reported "administered ever prior to hospital admission."

Abbreviation: CPR – Cardiopulmonary Resuscitation; CO_2 – Carbon Dioxide; CI – Confidence Interval; RA – Rearrest.

Table 4. Logistic Regression Model #1 - General Model

Predictor	OR	p	95% CI
Age	1.02	0.75	0.90 - 1.15
Male	1.02	0.89	0.79 - 1.30
Public Location	1.32	0.07	0.98 - 1.77
EMS Witnessed	1.35	0.16	0.89 - 2.04
First Rhythm VF/VT	0.57	< 0.00	0.40 - 0.80
Non-Cardiac Cause	0.87	0.60	0.53 - 1.45
Median Income	1.17	< 0.00	1.05 - 1.30
Time to EMS CPR	1.12	0.19	0.94 - 1.34
Time to ROSC	0.78	0.02	0.64 – 0.96
Time to Transport	1.19	0.01	1.04 - 1.37
Defibrillation	2.01	< 0.00	1.45 - 2.79
Pacing	1.42	0.11	0.92 - 2.18
Amiodarone	1.27	0.26	0.84 - 1.92
Atropine	1.97	< 0.00	1.42 - 2.74
Epinephrine	1.28	0.24	0.85 - 1.92
Source: CPR Process	0.71	0.04	0.51 - 0.98
Source: Signal	2.10	< 0.00	1.52 - 2.91

Note: Median Income modeled as quartiles. Time intervals and Age modeled in standard deviation-scaled units.
Abbreviation: ALS – Advanced Life Support, CPR – Cardiopulmonary Resuscitation, EMS – Emergency Medical Services, OR – Odds Ratio, RA – Rearrest, VF/VT – Ventricular Fibrillation / Ventricular Tachycardia.

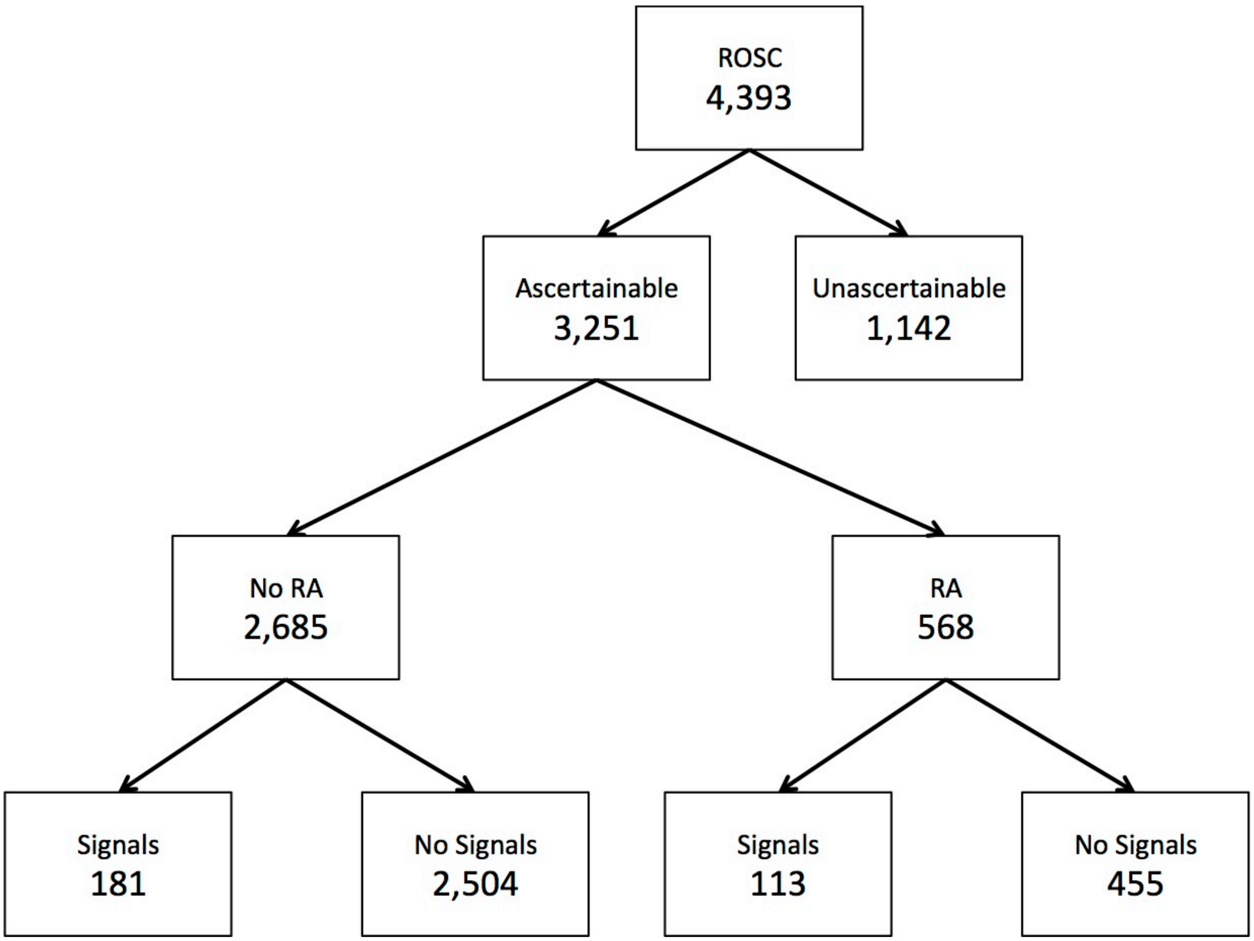
Table 5. Logistic Regression Model #2 - Causal Model

Predictor	OR	p	95% CI
Age	1.03	0.61	0.92 - 1.15
Male	1.07	0.58	0.85 - 1.33
Public Location	1.14	0.33	0.88 - 1.47
EMS Witnessed	1.31	0.14	0.91 - 1.89
First Rhythm VFVT	0.92	0.48	0.74 - 1.15
Non-Cardiac Cause	0.66	0.07	0.42 - 1.04
Median Income	1.14	0.01	1.04 - 1.26
Time to EMS CPR	0.95	0.42	0.82 - 1.08
Time to ROSC	1.10	0.07	0.99 - 1.22
Source: Signal	2.78	< 0.00	2.09 - 3.70
Source: CPR Process	0.59	< 0.00	0.45 - 0.76

Note: Median Income modeled as quartiles. Time intervals and Age modeled in standard deviation-scaled units.

Abbreviation: ALS – Advanced Life Support, CPR – Cardiopulmonary Resuscitation, EMS – Emergency Medical Services, OR – Odds Ratio, RA – Rearrest, VF/VT – Ventricular Fibrillation / Ventricular Tachycardia.

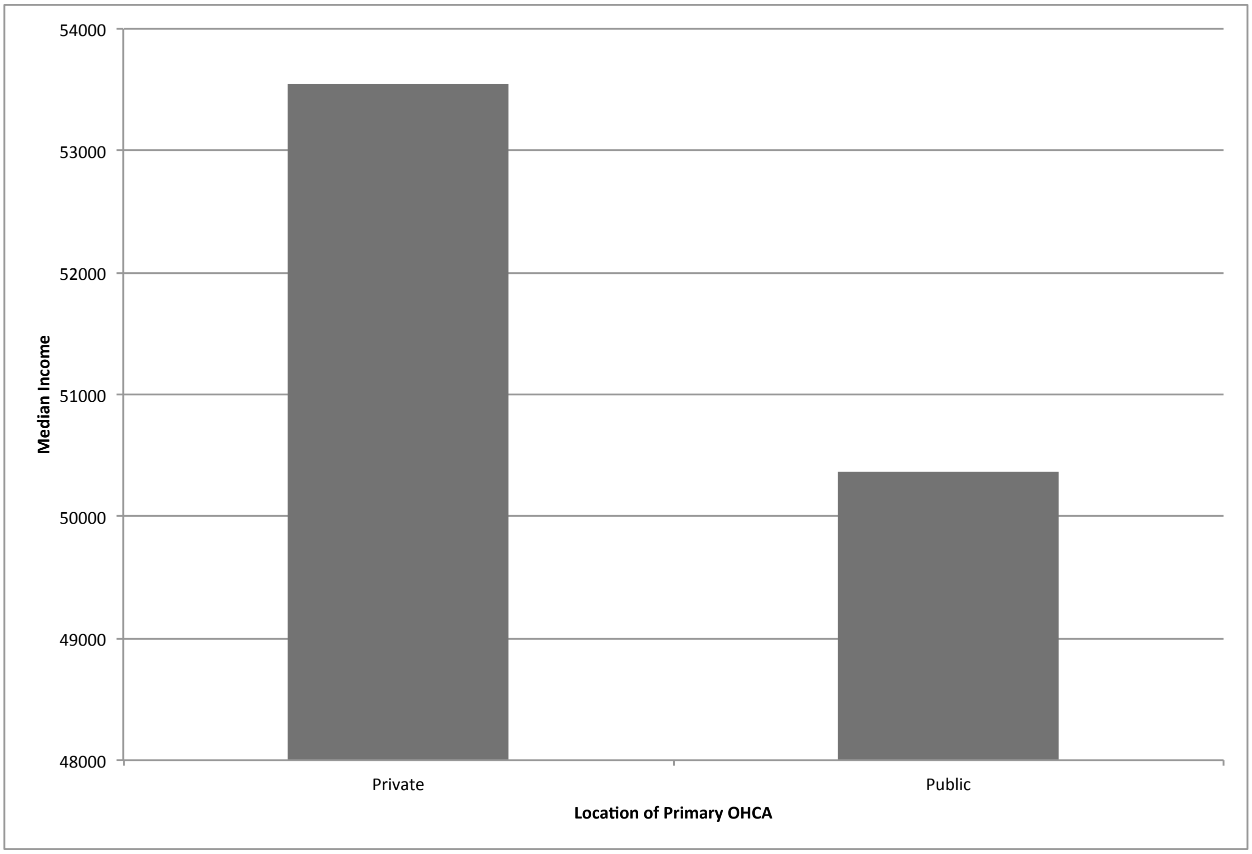
4.8 FIGURES



Note: Signals – Cases with available signal-derived characteristics.

Abbreviations: RA – Rearrest; ROSC – Return of Spontaneous Circulation.

Figure 1. Cohort Flow Diagram Showing Case Data Availability at Multiple Stages of Analysis



Note: Income is plotted as mean for each stratum and reported in US Dollars.

Abbreviations: OHCA – Out-of-Hospital Cardiac Arrest

Figure 2. Median Income Stratified by Location of Primary OHCA Event

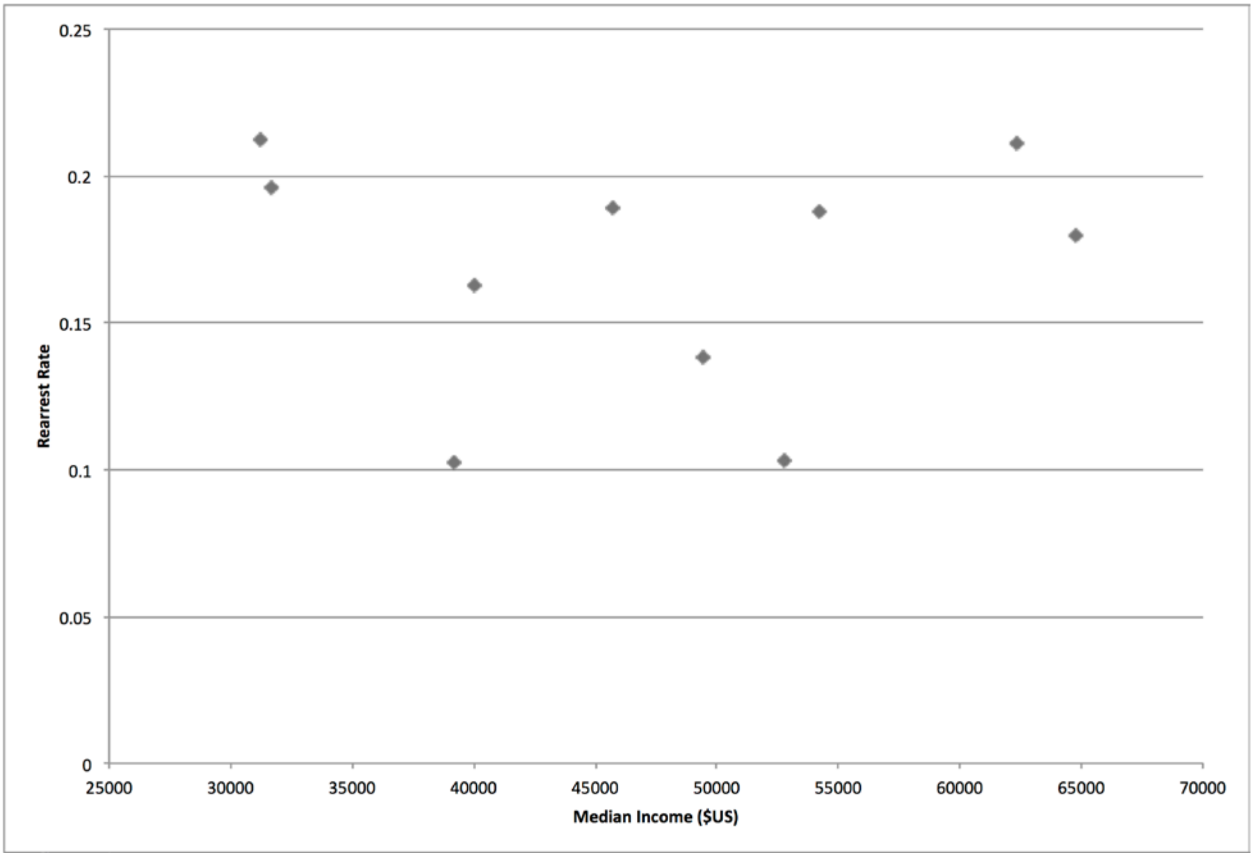
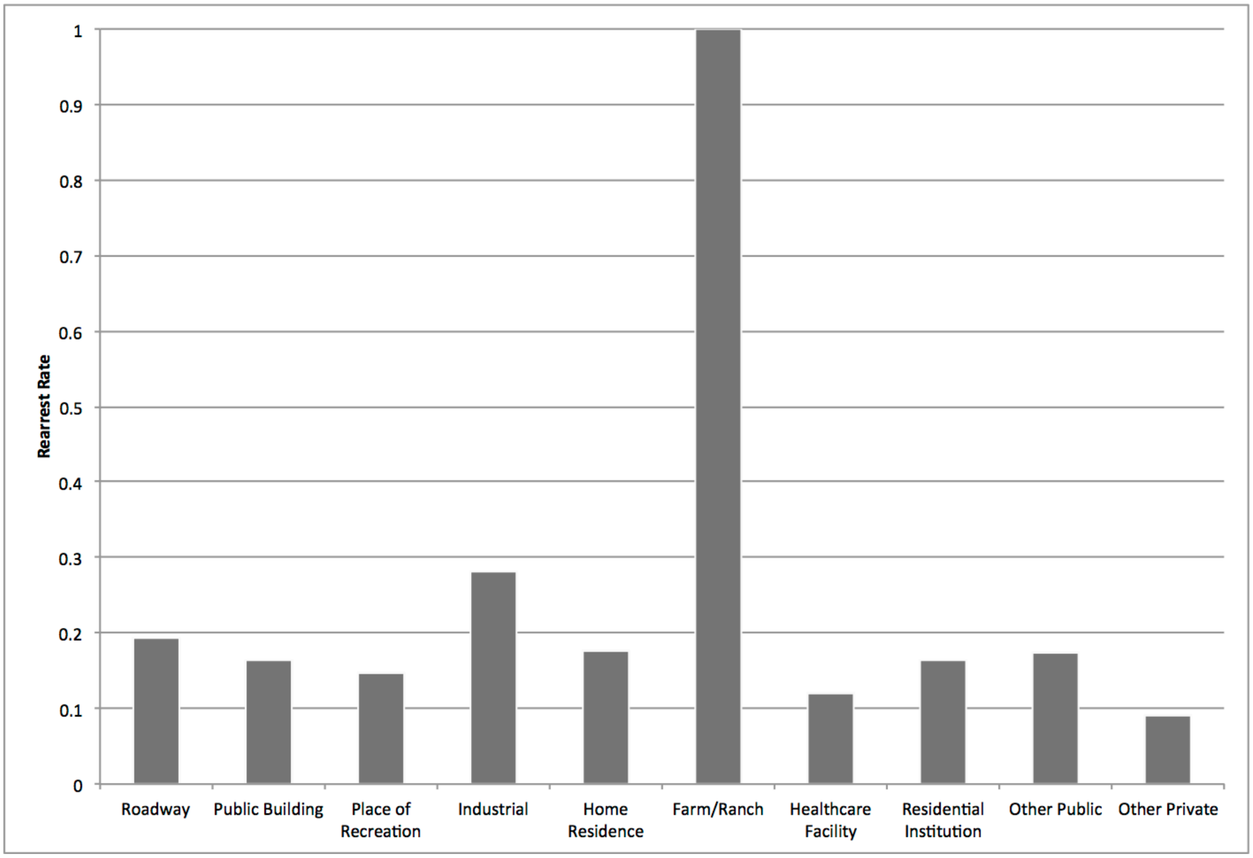


Figure 3. Site Rearrest Rate by Site Average Median Income



Note: Event total for category Farm/Ranch = 1

Figure 4. Rearrest Rate Stratified by Type of Location

5.0 ELECTROCARDIOGRAPHIC CHARACTERISTICS ASSOCIATED WITH REARREST AFTER OUT-OF-HOSPITAL CARDIAC ARREST

To be submitted for publication

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5.1 ABSTRACT

BACKGROUND/AIMS: Rearrest (RA) after resuscitation from out-of-hospital cardiac arrest (OHCA) has been shown to be an independent predictor of death before hospital discharge. Several procedural and patient factors have been shown to be associated with RA. The present study was conducted in order to determine whether features of the electrocardiogram (ECG) differ between cases with and without RA.

METHODS: Case data and defibrillator download files from 294 OHCA patients treated by emergency medical services who had achieved return of spontaneous circulation (ROSC) were obtained through the Resuscitation Outcomes Consortium from the years 2006 to 2008. Of these, 208 had analyzable ECG signals. RA was identified in 81 cases through analysis of defibrillator ECG and cardiopulmonary resuscitation (CPR) process data streams. In all cases, the ECG was analyzed for the period up to five minutes following first ROSC ("post-ROSC"). ECG was reviewed manually for qualitative features including atrial fibrillation / flutter, transient ventricular tachycardia, heart block, presence of premature ventricular complexes (PVCs), Q-waves and bigeminy/trigeminy. Quantitative characteristics were also calculated, including heart rate, QT interval, and measures of heart rate variability. Characteristics were compared between cases with and without RA. Multiple logistic regression was used to test the independent association between ECG features and the outcome of RA.

RESULTS: RA and no-RA cases differed by witnessed status (18.5% vs 7.1%), but not age, sex, race, public location, or presenting ECG rhythm. RA cases did not differ from no-RA cases by any qualitative features. Several quantitative characteristics differed between RA cases and no-

RA cases in univariate analyses. In multiple logistic regression models, only measures derived from QT interval were predictive of RA.

CONCLUSIONS: Quantitative ECG characteristics may be useful in discriminating between cases with and without RA.

5.2 INTRODUCTION

Successful resuscitation measures during out-of-hospital cardiac arrest (OHCA) result in return of spontaneous circulation (ROSC) but do not necessarily correct the underlying cause of the cardiac arrest nor ameliorate the relevant risk factors for another event. Patients therefore remain vulnerable to a subsequent cardiac arrest, or *rearrest* (RA), prior to and beyond admission to the hospital. In previous work including our own, the incidence and outcomes of RA have been estimated[49-52,59], and patient, circumstantial, and health care provider characteristics have been investigated as potential risk factors for RA[68]. In large, multi-region cohort of emergency medical services (EMS)-treated OHCA patients, having an RA event was found to be associated with a higher probability of death prior to hospital discharge, and the probability of experiencing an RA event was found to be related to patient characteristics, treatments and treatment intervals.

To date, previous work provides little physiological insight into the characteristics that differentiate cases with RA from those without RA [69-72]. However, physiological characteristics may provide the critical mechanistic insight necessary to predict and treat RA. Features of the electrocardiogram (ECG) may be the most relevant and most universally measurable features in OHCA patients given that they describe the activity of the most relevant organ system to OHCA and because ECG is ubiquitous in EMS systems throughout the developed world. Furthermore, there is precedent for the use of ECG analysis, including heart rate variability analysis, in patient risk stratification, as it has been previously used to predict mortality following myocardial infarction, trauma and sepsis, to name a few conditions etiologically relevant to OHCA[76-81]. Importantly, ECG is especially relevant to RA as it is the most likely data modality through which RA would be detected by prehospital health care providers, through manifestation of the obvious lethal ECG presentations of ventricular fibrillation (VF), ventricular tachycardia (VT), or asystole.

In the present study, a number of features available in the continuous prehospital ECG of OHCA patients successfully achieving ROSC were examined, with the hypothesis that these features could differentiate cases of OHCA that experienced RA from those that did not.

5.3 METHODS

The University of Pittsburgh Institutional Review Board approved this retrospective study. Case data for EMS-treated OHCA patients were obtained from the Resuscitation Outcomes Consortium (ROC), a multi-site clinical research consortium investigating OHCA and severe trauma in 11 regions in the United States and Canada. Cases included in this study were originally collected from the period spanning January 2006 to December 2008, through the population-level OHCA surveillance operations of the ROC in 10 of the 11 participating sites, in cooperation with local EMS agencies. Case data included patient demographic characteristics, provider treatment and timing variables, and defibrillator data files downloaded after resuscitation. Multi-modal defibrillator download data included at a bare minimum ECG and transthoracic impedance, sometimes supplemented by end-tidal carbon dioxide, and chest compression performance signals including continuous chest compression depth and chest compression force. Because this study was concerned with characteristics of the ECG, only cases with available and analyzable ECG channels in the defibrillator download files were included. In order to understand any biases associated with the absence of analyzable ECG, non-ECG characteristics of cases with and without ECG were compared in a subanalysis reported in this paper.

Data from defibrillator downloads were exported from native defibrillator file formats (Philips / Physio-Control / Zoll) and imported into a custom analytical environment programmed in Matlab (version 7.12.0 R2011a, Mathworks, Natick, MA). ROSC and RA status were determined through methods described in detail in a previous paper[59]. In brief, ROSC was identified in the signal data of the defibrillator download file as a period of non-lethal ECG rhythm in the absence of chest compressions and lasting at least one continuous minute. RA was identified as a lethal arrhythmia and/or resumption of chest compressions (lasting at least 1 minute) following ROSC.

All analyses in the present study were conducted on ECG from the treatment phase following first instances of ROSC only. That is, subsequent ROSC periods following additional resuscitation efforts were not analyzed. The complexity of such analysis warranted a separate treatment, reported elsewhere. ECG characteristics were assessed for the immediate post-ROSC 5-minute period in cases with and without RA, referred to hereafter as the post-ROSC period. This time period was chosen to force some temporal comparability/limitation since it is known that time-to-first-RA may vary greatly between patients and because, particularly in the case of non-RA patients, time from ROSC to hospital admission varied substantially. Furthermore, the 5-minute periods under consideration could and frequently did have some overlap. In cases with less than 5 minutes of analyzable ECG between ROSC and RA, the analytical period encompassed what amount of time was available.

Single-lead ECG was parsed into individual beats with custom software, beginning with automated R-wave detection by adaptable R-slope threshold. The RR time series was calculated from the series of successive R-wave times. QT-interval (QT) was estimated as the time interval between the start of the R-wave and the local zero in slope on the tail end of the T-wave. RT interval (RT_{apex}) was estimated as the distance between the apex of the R-wave and the apex of the T-wave[82-83]. It should be noted that prehospital continuous ECG is often heavily filtered by defibrillator/monitor hardware and software to preferentially express the QRS complex and suppress the P and T waves. This preprocessing makes analyses involving the T-wave in such data difficult. Thus, a method was employed for detecting the T-wave that had high sensitivity to low amplitude peaks. The T-wave itself was detected automatically as the largest peak following the R-wave with a minimum amplitude of $1/20^{th}$ the R-wave amplitude within 80 samples of the R-wave in the smoothed post-R region of each beat. Beats without detectible T-waves were automatically flagged, as were beats with T-waves but incalculable T-wave ends.

A battery of quantitative characteristics was calculated in 1-minute epochs for each post-ROSC period. These included direct measurements of the ECG, including heart rate (HR) derived from the RR time series, HR corrected QT interval (QTc; QT/sqrt(RR)), and as mentioned before, RT_{apex}. One measure of the variability of HR and one measure of its complexity were calculated: root mean square of the successive differences of the RR intervals (HR-RMSSD) and the approximate entropy of the same (HR-ApEn). RMSSD is a commonly used time domain heart rate variability measure corresponding to high frequency fluctuations in HR[84]. Approximate entropy is a non-linear measure of the randomness/complexity of time series data that has been applied previously to heart rate analyses[85]. Higher ApEn values reflect greater randomness in a time series. In this study, a parameter of m = 1 and r = 0.2*stdev(HR) was applied for each ApEn calculation, as is commonplace for HR analyses. Additionally, a "delta" (Δ) measure was calculated for each of the 5 measures above, taking the difference between the last and first available 1-minute epoch value in each of the measures. Essentially, these measures reflected the change from start to finish of each measure within each 5-minute measurement period.

Qualitative characteristics included assessment of the presence of premature ventricular contractions (PVC), apparent atrial fibrillation or flutter, obvious Q-waves, transient VT, bigeminy/trigeminy, and heart block. ST-depression and ST-elevation were not reliably ascertainable due to signal filtering, and so could not be reported with confidence. Qualitative measures were visually assessed in 30-second frames by one reviewer (DDS) as present or not present before being aggregated into 1-minute epochs.

Normally distributed continuous variables were compared between RA and no-RA cases with two-tailed t-tests. A normal approximation for comparison of proportions was used to compare dichotomous variables between RA and no-RA groups. Continuous ECG measures were compared between RA and no RA groups with 2-tailed t-tests or, if non-normally distributed, the Kruskal-Wallis test. Multivariable logistic regression was used to determine the independent association of ECG characteristics and RA status. In the first model, QTc derived measures were included, while in the second model RT derived measures were substituted in their places. Both models included age, sex, and EMS witness status. An alpha of 0.05 was used for all statistical analyses, and all statistical calculations were performed with Stata 12 (StataCorp, College Station, TX).

5.4 RESULTS

A total of 294 signals were available for ECG analysis from a previous related study. Of these, 208 cases were analyzable in the immediate post-ROSC period. Of those signals that were not analyzable, pervasive noise during the time frame of interest, cardiac pacing, data file corruption, and non-interpretable ECG structures were the causes for exclusion.

Table 6 summarizes the patient and OHCA characteristics of the cases included in the analysis. The proportion of cases with RA was 38.9%, with RA manifesting in 45.7% as VF, 23.5% as VT, 27.2% as pulseless electrical activity (PEA), and 3.7% as asystole. Cases with and without RA differed only on EMS-witnessed status; those with RA were more than twice as likely to have been witnessed by EMS personnel. Survival was not significantly different between the RA and no-RA groups. Age, sex, bystander witnessed status, and initial cardiac arrest rhythm were equivalent between both groups. Additionally, when the same characteristics were compared between those cases with analyzable ECG and those without (i.e., excluded from the study), cases with analyzable ECG had a significantly higher proportion of VF/VT initial OHCA ECG rhythm and a lower median income. Results of this sub-anlaysis are shown in Appendix B.

Table 7 shows the results of qualitative analysis of ECG in the post-ROSC period stratified by RA status. The most commonly observed qualitative characteristic was PVC (18.8%). RA cases did not differ from no-RA cases by any of the qualitative measures.

Table 8 shows the results of quantitative analysis of continuous ECG measures, stratified by RA status. RA cases showed a significantly lower post-ROSC HR than no-RA cases (p =

0.045). RA cases also showed significantly lower ΔRT_{apex} ($p = 0.001$) and ΔQTc ($p < 0.001$) than no-RA cases. Other measures did not differ between the 2 groups.

In the logistic regression model containing QT-derived measures, ΔQTc was significantly inversely ($p = 0.004$, OR: 0.005, 95%CI: 0.000 – 0.170) related to RA case status. In the model containing RT-derived measures, ΔRT_{apex} was also significantly inversely ($p = 0.005$, OR: 0.0001, 95%CI: 0.000 – 0.054) related to RA case status. No other covariates were significantly related to RA status in either model. Post-estimation receiver operating characteristic analysis indicated areas under the curve of $c_{QTC\_Model} = 0.67$ and $c_{RTApex\_Model} = 0.68$ indicating poor-to-fair predictive accuracy. Hosmer-Lemeshow Goodness-of-Fit tests of both models did not indicate poor model-fitting ($p_{QTC\_Model} = 0.24$ and $p_{RTApex\_Model} = 0.42$). See Appendix C for plots of predicted probability of RA modeled separately on ΔQTc and ΔRT_{apex} in univariate logistic regression analyses.

5.5 DISCUSSION

There are two general messages to be taken from the results of this limited study. First, as hypothesized, it is possible to use at least one feature of the post-resuscitation, prehospital ECG to differentiate RA cases from no-RA cases. In univariate analyses, several continuous measures, although no qualitative measures, were useful. In the final multivariable model, only one measure at a time was predictive of RA. This is not unreasonable, given that continuous measures considered in this study were derived entirely from HR, either directly or via a mechanism that is linked to HR, i.e. repolarization time, embodied by RT_{apex} and QTc.

There is limited opportunity for comparison of these findings with the extant RA literature given that preceding studies are generally contextualized to the post-hospital admission phase of survival. During this period, patients have likely experienced treatments, procedures, and progressive physiological changes that cannot be directly compared to freshly resuscitated patients who have yet to be admitted to hospital. For the sake of comparison, Shaffer et al and Weaver et al both investigated ECG indicators that predispose patients to recurrent VF during long term follow-up in OHCA survivors[69-70]. Schaffer et al found that a presenting OHCA rhythm of VF predisposed patients to earlier RA, while Weaver et al observed that several ECG features collapsed into the category of complex ectopy were associated with a greater than 2-fold risk of subsequent cardiac arrest in some OHCA survivors. Neither study considers measures of heart rate variability. Russell analyzed characteristics of the VF ECG waveform in patients with refibrillation, finding that VF characteristics correlated with survival outcomes, though not explicitly with any qualities of the refibrillation events themselves.

The second message is that differentiation between RA cases and no-RA cases can apparently occur relatively early after successful resuscitation and relatively proximal to RA. The 5-minute post-ROSC period falls near the median of the first ROSC-to-RA time observed in this group (4.4 minutes)[59]. Unfortunately, the present study does not reveal how quickly within that period impending RA can be discerned; it merely implies that there is relevant information in the ECG during that period.

In this study, derivations of QT interval and a circumstantially more useful surrogate of QT interval, RT interval, were found to predict RA during the immediate post-ROSC period. Additionally, the direction of the observed association suggests that RA cases tend to exhibit a decrease in QT interval in the early post-ROSC period. While there is precedent for QT interval in prediction of sudden death[86], the link in this case is not straightforward, as the observed associations reflect not absolute interval length but changes in interval length. Moreover, in this study these particular measures were difficult to ascertain due to signal condition. While there is reasonable confidence that differences in recording conditions did not result in the observed differences between RA and no-RA cases, a tentative position must be taken until these findings can be replicated with diagnostic-quality ECG. Of course, the clinical utility of the observed associations remains to be seen as well. Even if a single mechanism underlies the relationship between QT-derived measures and RA, an assumption that seems vanishingly unlikely in the face of the multiple ECG presentations of OHCA, there may be no obvious mode of intervening. On that note, one might reasonably suspect that if there were a unifying characteristic between RA cases that differentiated these cases from cases without RA, it might actually be a downstream consequence of some intervention, less than a consequence of a specific common pathology.

The limitations of this study largely result from the reliance on prehospital data. Little to no patient history, such as cardiovascular conditions or medications, was available. Similarly, only limited patient follow up was available, not including relevant procedures performed after hospital admission. The ECG signal relied upon for this study is not standard diagnostic ECG, seriously limiting the techniques available for its characterization. Moreover, signal was often noisy due to motion artifact, poor lead contact, and other unknown sources, making complete characterization difficult. Finally, the present study draws from an existing retrospective cohort of several thousand patients, to which the authors were given access by the ROC. However, during the capture period routine retention of continuous ECG files was very rare in the Consortium, resulting in an unfortunately low sample size for the signal analysis arm of this study. It is likely that the present analyses were greatly under-powered, and not representative of the full diversity of OHCA patients and presentations.

5.6 CONCLUSIONS

In the period immediately following first ROSC, ΔRT_{apex} and ΔQTc were predictive of RA. No qualitative measures of the ECG were associated with RA.

5.7 TABLES

Table 6. Case Characteristics of Cases with Signals, Stratified by Rearrest Status

Characteristic	Overall	RA (-)	RA (+)	p
Age, y	61.9 (17.5)	61.1 (17.7)	63.2 (17.3)	0.408
Male, %	63.9% (57.4 – 70.5)	65.4% (57.1 – 73.6)	61.7% (51.1 – 72.3)	0.595
Median Income, $US	48959 (17312)	48026 (16715)	50353 (17758)	0.364
Public Location %	25.5% (19.5 – 31.5)	28.3% (20.5 – 36.2)	21.0% (12.1 – 29.9)	0.235
Bystander Witnessed %	65.6% (58.5 – 72.6)	67.0% (58.4 – 75.5)	63.1% (51.3 – 74.8)	0.599
EMS Witnessed %	11.5% (7.2 – 15.9)	7.1% (2.6 – 11.5)	18.5% (10.1 – 27.0)	0.012
First ECG Rhythm VF/VT %	52.4% (45.6 – 59.2)	52.0% (43.3 – 60.7)	53.1% (42.2 – 64.0)	0.875
Non-Cardiac Cause, %	4.8% (1.9 – 7.7)	5.5% (1.5 – 9.5)	3.7% (0 – 7.8)	0.552
Time to EMS CPR, minutes	10.4 (8.6)	10.3 (8.4)	10.4 (9.0)	0.893
Time to ROSC, minutes	24.7 (12.1)	23.9 (11.3)	26.0 (13.3)	0.240

Note: Age, Median Income and Time Intervals reported as mean (standard deviation). All others reported as %, (95% confidence interval).
Abbreviations: CPR – Cardiopulmonary Resuscitation; ECG – Electrocardiogram; EMS – Emergency Medical Services; ROSC – Return of Spontaneous Circulation; RA – Rearrest; VF/VT – Ventricular Fibrillation / Ventricular Tachycardia.

Table 7. Qualitative ECG Characteristics Stratified by Rearrest Status

Characteristic	Overall	RA (-)	RA (+)	p
AFib/AF, %	10.6 (2.1)	12.6 (2.9)	7.4 (2.9)	0.235
Q-Waves, %	6.3 (1.7)	7.9 (2.4)	3.7 (2.1)	0.226
VT, %	4.3 (1.4)	3.1 (1.5)	6.2 (2.7)	0.296
Bigem/Trigem, %	3.8 (1.3)	2.4 (1.3)	6.2 (2.7)	0.164
PVC, %	18.8 (2.7)	22.8 (3.7)	12.3 (3.7)	0.059
Block, %	10.1 (2.1)	7.9 (2.4)	13.6 (3.8)	0.183

Note: All characteristics in percent (standard error) of cases in which they were observed.
Abbreviations: AFib – Atrial Fibrillation; AF – Atrial Flutter; Bigem/Trigem – Bigeminy / Trigeminy; PVC – Premature Ventricular Contraction; RA – Rearrest; VT – Ventricular Tachycardia (transient).

Table 8. Quantitative ECG Characteristics Stratified by Rearrest Status

Characteristic	RA (-)	RA (+)	Overall	p
Heart Rate, BPM	125.7 (29.4)	116.3 (37.4)	122.0 (33.0)	0.045
ΔHeart Rate, BPM	9.4 (30.3)	5.9 (40.8)	8.1 (34.7)	0.481
HR-RMSSD, s	0.25 (0.35)	0.21 (0.19)	0.23 (0.30)	0.887*
ΔHR-RMSSD, s	0.05 (0.71)	-0.01 (0.43)	0.02 (0.61)	0.522
HR-ApEn, AU	1.01 (0.39)	0.93 (0.39)	0.98 (0.39)	0.133
ΔHR-ApEn, AU	-0.01 (0.52)	-0.08 (0.59)	-0.03 (0.55)	0.401
RT_{apex}, s	0.19 (0.05)	0.19 (0.05)	0.19 (0.05)	0.720
ΔRT_{apex}, s	0.01 (0.05)	-0.01 (0.05)	0.00 (0.05)	0.001
QTc, s	0.42 (0.08)	0.39 (0.09)	0.41 (0.08)	0.059
ΔQTc, s	0.03 (0.08)	-0.02 (0.11)	0.00 (0.09)	<0.001

Abbreviations: ApEn – Approximate Entropy; HR – Heart Rate; RMSSD – Root Mean Square of Successive Differences; s – Seconds.
Note: * - Non-parametric test used.

6.0 TOWARDS PREDICTING THE TIMING AND RHYTHM OF REARREST AFTER OUT-OF-HOSPITAL CARDIAC ARREST

To be submitted for publication

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6.1 ABSTRACT

BACKGROUND/AIMS: Rearrest (RA) after resuscitation from out-of-hospital cardiac arrest (OHCA) has been shown to be an independent predictor of death before hospital discharge. The ability to anticipate RA and its consequences could increase survival to hospital discharge after OHCA. The aim of this study was to understand how heart rate and rhythm transitions relate to the timing and presentation of rearrest.

METHODS: Case data for emergency medical services (EMS)-treated OHCA were obtained from the Resuscitation Outcomes Consortium (ROC) for the period 2006-2008. Cases with analyzable electrocardiogram (ECG) signals were included in the study. For each case, return of spontaneous circulation (ROSC) events were identified by an inferential scheme involving the presence of non-life-threatening ECG rhythm and absence of chest compressions. Downstream of each ROSC event, potential RA events were ascertained by an inferential scheme involving the presence of a life-threatening ECG rhythm and/or presence of chest compressions. All identified ROSC-RA ECG intervals were extracted from original defibrillator source files and imported into custom software for calculation of several heart rate characteristics for 30s, 1min, 3min, and 5min epochs beginning at the onset of ROSC, including: mean heart rate, standard deviation for heart rate (SD-HR), root mean square of the successive differences (RMSSD), and approximate entropy of heart rate (ApEn). If sufficient data were available (3min or 5min), frequency-based heart rate variability measures including normalized high frequency power (HFN), normalized low frequency power (LFN), and ratio of low and high frequency power (LFHF) were calculated. The relationship of individual heart rate characteristics to time-to-RA was assessed with univariate regression analysis. Multivariable generalized estimating equations

(GEE) were used to assess the relationship between heart rate characteristics and time-to-RA while controlling for RA event number, presenting OHCA ECG rhythm, and RA ECG rhythm. Rhythm transitions were assessed and compared with Fisher's exact test.

RESULTS: In univariate analyses RMSSD in the 30s and 1-minute epoch epochs, SD-HR in the 5-minute epoch, ApEn in the 5-minute epoch, presenting ECG rhythm ventricular fibrillation / ventricular tachycardia (VF/VT), and RA event number were predictive of time-to-RA. In a multivariable model, only SD-HR in the 5-minute epoch was related to time-to-RA (coeff. = -764.16; 95%CI: -1405.92 , -122.40; p = 0.020). The most common first rhythm transition was from VF/VT to VF/VT.

CONCLUSIONS: At least one heart rate-derived measure, SD-HR, was related to time-to-RA event, independent of RA ECG rhythm, presenting OHCA ECG rhythm or RA event number.

6.2 INTRODUCTION

Rearrest (RA) is the recurrence of cardiac arrest following successful resuscitation and occurs prior to hospital admission in at least 15% of successfully resuscitated cases of out-of-hospital cardiac arrest (OHCA)[49,51,59]. While many patients with RA may be successfully admitted to hospital, RA has been strongly correlated with death prior to hospital discharge[59]. Few factors have been shown to correlate with occurrence of RA, although in previous study (Section 4) median income was shown to predict RA and some procedural and timing factors were associated with RA.

The next logical steps in understanding RA involve the examination of factors that give insight into the temporal proximity of an impending RA, the clinical manifestation of RA, and the consequences of a given clinical manifestation of RA. Information about temporal proximity is essential to prediction but critically important to treatment as well. If a provider were to know soon after return of spontaneous circulation (ROSC) that the patient was likely to experience an RA within 2 minutes, her or she may forego pharmacological interventions and instead charge a defibrillator. Clinical manifestation of RA is critical as well. The same provider would prepare for chest compressions instead of defibrillation if he or she knew that the impending RA would be asystole, not ventricular fibrillation (VF). Lastly, the information about the consequences of a given presentation of RA could influence downstream decisions, including withdrawal of care.

ECG analysis presents a readily translatable means of considering the three aforementioned concerns. ECG is ubiquitous in the treatment of OHCA in the developed world, and advances in ECG monitor technology have served a critical role in the management of cardiovascular disease [87-89]. Moreover, previous evidence (Section 5) exists to indicate that ECG signal characteristics differ between cases with and without RA, from which one might reasonably infer that similar differences may manifest between ECG proximal to RA and ECG more temporally distant. Previous studies have also sought to characterize the nature and utility of rhythm transitions during treatment of OHCA[90-91]. There is some evidence in these studies to suggest that the specific presentation of these transitions is multifactorial and that key transitions may affect survival. More detail in the context of RA may clarify these relationships.

The present study was conducted in order to investigate whether measures derived from a readily accessible ECG property, heart rate, as well as ECG rhythm transitions could be used to determine when and how RA will manifest, as well as the downstream consequences of a given RA event. It was hypothesized that measures derived from heart rate would correlate with time-to-RA and the ECG presentation of RA.

6.3 METHODS

The University of Pittsburgh Institutional Review Board approved this retrospective study. Case data for emergency medical services (EMS)-treated OHCA were acquired from the Resuscitation Outcomes Consortium (ROC). The ROC is a multi-site clinical research consortium with 11 sites in the US and Canada conducting population-level surveillance of OHCA incidence, outcomes and related health services, as well as clinical trials to assess emergency interventions for OHCA and life-threatening trauma. Case data included patient demographics, condition, treatments and treatment timing extracted from patient care reports and computer assisted dispatch records, as well as defibrillator/monitor data files when available. The cohort used in the present study has been described in depth previously, however a basic summary follows. All cases of EMS-treated OHCA captured by the ROC between 2006 and 2008, prior to the beginning of a consortium-wide interventional trial, were screened for the presence of ROSC prior to hospital admission. Cases fitting this initial criterion were then analyzed for evidence of RA by a three-fold ascertainment scheme incorporating direct signal analysis, indirect signal analysis, and record review. Cases identified as having RA were included if analyzable signals were available, where "analyzable" denotes ECG signals without sufficient noise as to obscure the QRS complex for the purpose of calculating heart rate. Defibrillator/monitor signals, including at a minimum ECG and transthoracic impedance, were extracted from proprietary defibrillator/monitor download files and converted into a uniform format on a single timeline for each case for analysis in a single platform.

For each case, ROSC was first identified manually through an inferential scheme considering the current ECG rhythm and presence or absence of chest compressions detectable in any of the defibrillator's signals. A minimum epoch of 1 minute of non-lethal ECG rhythm occurring in the absence of chest compressions was required in order to be considered ROSC. Downstream RA was subsequently determined manually in a similar manner with attention to the presence of lethal ECG rhythm, the resumption of chest compressions and/or the delivery of a defibrillating shock, where the duration of inferred RA was required to be a minimum of 1 minute in order to be considered a true RA. Multiple instances of RA in a single case were classified as RA-1, RA-2, RA-3 and so forth, where each was associated with its immediately preceding ROSC event, classified as ROSC-1, ROSC-2, ROSC-3 and so forth.

ECG signal from each ROSC-i event to its associated RA-i event was isolated for analysis. R-waves were identified in each span through slope analysis, and a continuous time series of RR intervals was constructed, from which beat-per-minute (BPM) heart rate could be derived by dividing 60 by each RR interval. Heart rate bins were constructed for the available 30-second, 1-minute, 3-minute and 5-minute epochs immediately preceding each RA event. For each epoch, mean, standard deviation (SD-HR), root-mean-squared of the successive differences (RMSSD), and approximate entropy (ApEn) of heart rate were calculated. For the 3- and 5-minute epochs, spectral analysis was conducted through an autoregressive Fourier transform analog[84]. Low and high frequency spectral components were calculated (LF & HF) and normalized by total power (LFN & HFN). The ratio of LF to HF (LF/HF) was then calculated from these two measures by simple division. LFN, HFN, and LF/HF could not be calculated reliably for shorter epochs due to the constraints of low frequency spectral analysis.

Kaplan-Meier survival plots were created to show survival over time, where observation began at each ROSC event and the failure event was the subsequent RA, both for all ROSC-RA intervals and stratified by several factors, including the ECG presentation of RA events, ECG presentation of the primary OHCA event, and sequential RA event number, bearing in mind that many ROSC-RA intervals were not the first event experienced by a given patient.

Generalized estimating equations (GEE) were used to assess the relationship between time to RA and heart rate characteristics, controlling for RA event number and RA ECG rhythm. It is again critical to note that individual event number and unique subject identifiers were utilized to control for within-subject correlation created by inclusion of multiple RA events from individual patients. Separate models were constructed for each of the time epochs in which a heart rate measure was significantly related to time-to-RA, in deference to the reality that clinical prognostication based on prehospital heart rate analysis would probably not mix data from overlapping time epochs, instead choosing a particularly relevant epoch for risk assessment.

Secondary rhythm transitions were defined as *the combined results of two consecutive ECG rhythm assessments take before and after an instance of ROSC*. For example, if a patient presented with an initial OHCA ECG rhythm of ventricular fibrillation / ventricular tachycardia (VF/VT), was resuscitated, and then rearrest into asystole / pulseless electrical activity (PEA), this secondary transition would be VF/VT-to-Asystole/PEA. *This definition will be used throughout the remainder of this paper.* A transition might refer to a rhythm change, as in the example, or a stable state between two consecutive rhythm assessments, again always with ROSC between rhythm assessments. The principle transition of interest was from the initial OHCA ECG rhythm to the first RA ECG rhythm. For transition analysis, rhythms were classified as ventricular fibrillation / ventricular tachycardia (VF/VT) or Asystole/Pulseless electrical activity (PEA) on the basis of indicated treatment, the former being treated with defibrillation and the latter generally non-responsive to defibrillation. The proportion of patients beginning in VF/VT and having a first RA of Asystole/PEA was compared to the proportion of patients beginning in Asystole/PEA and having a first RA of VF/VT using a two-tailed Fisher's exact test.

All statistical analyses were conducted in Stata 12 (StataCorp, College Station, TX) with an alpha level of 0.05 as the criterion of statistical significance unless otherwise specified.

6.4 RESULTS

A total of 133 ROSC-RA events were available and analyzable from 83 individual cases. Table 9 summarizes the patient, condition and treatment characteristics of these cases. Sixty-two percent of these were first RA events, 56.4% overall had a primary OHCA presentation of VF/VT and 69.9% overall had an RA presentation of VF/VT. Figure 5 shows the distribution of time-to-RA across all available intervals. The mean (SD) time from ROSC to RA was 5.5 minutes (5.9) overall, 6.8 minutes (6.9) for first RA events, and 3.7 minutes (2.9) for subsequent RA events collectively. A total of 25 cases had more than 1 RA event (range: 1 to 8) with a median (IQR) of 1 (1-2) event per case overall.

Figure 6 shows the Kaplan-Meier plot for all intervals together, as well as intervals stratified by event order, primary OHCA rhythm, and RA rhythm. Overall, 50% of RA events occurred within 3 minutes of the preceding ROSC event and 75% within approximately 7 minutes.

Table 10 shows the results of the heart rate analyses stratified by analytical epoch and RA ECG presentation. Only ApEn in the 1-minute epoch differed ($p = 0.035$) between RA events with VF/VT and Asystole/PEA ECG presentations.

In univariate regression analyses including all RA events, presenting ECG rhythm VF/VT (coeff = -139.7, $p = 0.025$), RA event number (coeff = -66.6, $p = 0.004$), and SD-HR in the 5-

minute epoch (coeff = -884.4, p = 0.019) were significantly associated with time-to-RA. When restricted to RA-1 for each case, presenting ECG rhythm of VF/VT (coeff = -198.9, p = 0.028), and SD-HR in the 5-minute epoch (coeff = -1083.5, p = 0.036) were associated with time-to-RA. However, when only subsequent RA events were considered, i.e. excluding RA-1, EMS witnessed status (coeff = 143.2, p = 0.010), RMSSD in both the 30-second (coeff = 771.2, p = 0.012) and 1-minute epochs (coeff = 1098.9, p = 0.003), and ApEn in the 5-minute epoch (coeff = 180.4, p = 0.019) were significantly associated with time-to-RA.

Results of multivariable GEE analyses are shown in Table 11. In Model 1, time-to-RA was modeled with EMS witness status, RMSSD in the 30-second epoch, presenting rhythm VF/VT, RA event number, and RA rhythm VF/VT. Only presenting rhythm VF/VT and RA event number were significantly associated with time-to-RA.

In Model 2, time-to-RA was modeled with EMS witnessed status, RMSSD in the 1-minute epoch, presenting ECG rhythm VF/VT, RA event number, and RA rhythm VF/VT. Once again, only presenting rhythm VF/VT and RA event number were significantly associated with time-to-RA.

In Model 3, time-to-RA was modeled with SD-HR in the 5-minute epoch, ApEn in the 5-minute epoch, presenting ECG rhythm VF/VT, RA event number, and RA ECG rhythm VF/VT. SD-HR in the 5-minute epoch and presenting ECG rhythm VF/VT were significantly, inversely associated with time-to-RA.

Figure 7 shows the frequency of each of 4 possible rhythm transitions, where the starting rhythm was the first observed ECG rhythm during OHCA and the ending rhythm was the ECG presentation of first RA. Transition from VF/VT to Asystole/PEA was the least common transition (12%), while the “stable” transition of VF/VT to VF/VT was the most common (42%).

The proportion of transition to Asystole/PEA from either rhythm category was not significantly different (p = 0.06). Please see Appendix D for tentative findings regarding transitions and survival to hospital discharge.

6.5 DISCUSSION

These results indicate that there may be at least one ECG feature, SD-HR, associated with impending RA events, independent of presenting OHCA ECG rhythm, RA event number, and ECG rhythm of RA event. As SD-HR increases, time-to-RA decreases, indicating that increasing variability in heart rate over the first 5 minutes following an ROSC event decreases the stability of the patient. This relationship only holds for RA events that follow ROSC by at least 5 minutes, and is not reflected in other common measures of variability or complexity. At the univariate level SD-HR was significantly directly associated with time-to-RA when only secondary RA events were considered, creating some uncertainty regarding the significance of the multivariable model findings. In the same multivariable model, ApEn in the 5-minute epoch was not significantly associated with time-to-RA, despite an observed univariate association, suggesting that the effect of ApEn in this sample was mediated by variability in heart rate.

Previous studies have shown the prognostic potential of heart rate variability in diverse conditional settings[76-81,92]. The presumptive mechanism underlying the results of these studies is the failure of the autonomic nervous system to maintain cardiac homeostasis in the face of pathological disruption of function[84]. The applicability of this general mechanism in the context of RA is unclear, considering the duration and conditions in which the ECG was analyzed. The median ROSC-to-RA interval in the present study was approximately 3 minutes and ECG recording conditions were sub-diagnostic, being heavily filtered to facilitate optimization of heart rate monitoring. More significantly, prehospital ECG recordings suffer from the introduction of incidental and procedural artifact into the recording. Coupled with no information about the patients' pre-OHCA medical history, it is difficult to speculate on the validity of heart rate variability measures to anticipate impending RA events. The finding that one measure was ultimately related to proximity of impending RA encourages concerted prospective RA studies in the vein of those conducted in the field of trauma. In prospective studies, it may arise that RA should really be viewed as an indicator of an inherent instability that reduces the probability of survival not in and of itself but due to underlying mechanisms that merely manifest in the prehospital environment as a loss of pulses.

Other critical findings from this study regard the concept of secondary rhythm transitions and their possible implications for treatment and survival. In this study, rhythm transitions did not necessarily follow consistently with the initial OHCA rhythm, although that was the tendency. This finding agreed with a limited previous RA study[49]. This particular transition heralds a lack of responsiveness to therapy or potentially an irreversible level of insult, and one might expect it to correlate with survival. At least 2 studies in the OHCA literature investigated transitions from Asystole/PEA to VF/VT, finding mixed results on the effect of this transition on survival to hospital discharge[93-94]. Specific consideration of the opposite transition is hard to find in the literature, likely because the former transition is a major treatment priority of initial Asystole/PEA, a state that if left unchanged has little therapeutic recourse.

This study provides a first look at the relationship between heart rate characteristics and all-rhythm RA and provides some grounds for future investigation, but it has several limitations. Principally this study suffers from a small sample size and by necessity, a constrained study design. In order to begin the investigation of factors that may predict RA, it was necessary to choose both a readily available study sample and study design that was amenable to the size and heterogeneity of the available data. Case data included in this study was derived from ROC surveillance in the period 2006 to 2008, limiting generalization to current times by virtue of changes to resuscitation guidelines, as well as secular trends in OHCA incidence, initial ECG rhythms, survival, in-hospital treatment, and surveillance efficiency.

An additional important limitation may have been possible unequal contribution of multiple events from individual patients. Given that some patients contributed more than one event to analyses, it may be that associations between the characteristics of those patients overwhelmed associations observable among patients with single events. The analytical design of this study attempt to avert imbalanced contribution by controlling for event sequence number in multivariable models, however one cannot discount the possibility that an imbalanced contribution remains. The significance of such an imbalance is non-trivial. As demonstrated by this study, some patients are apparently more likely than others to experience multiple RA events. If this is a manifestation of differing underlying pathology, then one should show caution in attempting to interpret predictive characteristics uniformly between the two types of patient.

Finally, it is worth paying particular note to the substantial limitation regarding patient history inherent in this and preceding work toward the understanding of RA. This limitation is not only a common condition in the great preponderance of prehospital research, but it reflects the reality of acute prehospital care and prehospital medical decision-making. The complete medical history of OHCA patients, even those details regarding etiologically relevant conditions, is seldom at hand throughout the duration of resuscitation or prehospital post-resuscitation care. This reality places a burden on the OHCA researcher, demanding ultimately one of two positions regarding the development of prognostic tools: acceptance or dismissal. To accept the acute focus required in the absence of patient historical data is to posit that there is some generalizable predictive utility in those data that present acutely after OHCA and that the effect of variability in immeasurable historical variables is not sufficient to obfuscate the effect of the former. This approach therefore depends on intense characterization of this acute condition and the willingness to conduct a metaphorical fishing expedition.

6.6 CONCLUSIONS

In multivariable models adjusting for presenting OHCA ECG rhythm, RA event number, and RA ECG rhythm, SD-HR ascertained in a 5-minute post-ROSC epoch was inversely associated with time-to-RA. Most often, RA events involved a secondary transition from VF/VT initial OHCA rhythm to VF/VT first RA.

6.7 TABLES

Table 9. Case Characteristics Stratified by First Rearrest ECG Rhythm

Characteristic	Overall	Asystole/PEA	VF/VT	p
Age, y	63.4 (17.4)	63.7 (17.7)	63.2 (17.3)	0.908
Male, %	62.4% (54.1 – 70.7)	47.5% (32.0 – 63.0)	68.8% (59.4 – 78.2)	0.020
Median Income, $US	50355 (17717)	49179 (19531)	50875 (17029)	0.705
Public Location %	18.8% (12.1 – 25.5)	7.5% (0 – 15.7)	23.7% (15.0 – 32.3)	0.029
Bystander Witnessed %	61.0% (51.5 – 70.4)	53.6% (35.1 – 72.0)	63.6% (52.9 – 74.4)	0.350
EMS Witnessed %	20.3% (13.4 – 27.2)	27.5% (13.7 – 41.3)	17.2% (9.5 – 24.9)	0.176
First ECG Rhythm VF/VT %	56.4% (47.9 – 64.9)	32.5% (18.0 – 47.0)	66.7% (57.1 – 76.2)	<0.001

Note: Age and Median Income reported as mean (standard deviation). All others reported as percent (95% confidence interval).
Abbreviations: ECG – Electrocardiogram; EMS – emergency medical services; PEA – pulseless electrical activity; $US – US Dollars; VF/VT – ventricular fibrillation / ventricular tachycardia.

Table 10. Heart Rate Characteristics Stratified by First Rearrest Rhythm

Characteristic	Asystole/PEA	VF/VT	Overall	p
1 minute epoch **n = 133**	-----	-----	-----	-----
Mean Rate, BPM	99.3 (32.3)	95.8 (36.2)	96.8 (35.0)	0.599
SD-HR, s	0.14 (0.11)	0.18 (0.13)	0.17 (0.13)	0.104
RMSSD, s	0.09 (0.05)	0.12 (0.07)	0.11 (0.07)	0.066
ApEn	0.66 (0.42)	0.86 (0.51)	0.80 (0.49)	0.035*

Note: Only the 1-minute epoch is shown due to consistent non-significance for all other time epochs. All measures are reported as mean (standard deviation). * - significantly different between asystole/PEA rearrests and VF/VT rearrests.
Abbreviations: ApEn – approximate entropy; BPM – beats per minute; PEA – pulseless electrical activity; RMSSD – root mean square of the successive differences; SD-HR – standard deviation of heart rate; VF/VT – ventricular fibrillation / ventricular tachycardia.

Table 11. Results of Multiple Regression Models Covering Separate Time Epochs

	Coefficient	95% CI	p-value
Model 1	------	------	------
RMSSD-30s	-180.21	-954.57 , 594.14	0.648
EMS Witnessed	79.72	-74.08 , 233.52	0.310
Presenting Rhx VF/VT	-136.24	-263.64 , -8.84	0.036
RA Event Number	-59.04	-104.33 , -13.75	0.011
RA Rhx VF/VT	-46.88	-180.07 , 86.30	0.490
Model 2	------	------	------
RMSSD-1min	66.18	-835.13 , 967.49	0.886
EMS Witnessed	73.63	-79.01 , 226.27	0.344
Presenting Rhx VF/VT	-135.61	-262.59 , -8.62	0.036
RA Event Number	-57.78	-103.28 , -12.29	0.013
RA Rhx VF/VT	-52.47	-185.97 , 81.02	0.441
Model 3	------	------	------
SD-HR-5min	-764.16	-1405.92 , -122.40	0.020
ApEn-5min	-31.96	-195.36 , 131.43	0.701
Presenting Rhx VF/VT	-231.22	-408.07 , -54.36	0.010
RA Event Number	-96.13	-200.95 , 8.69	0.072
RA Rhx VF/VT	-164.01	-355.20 , 27.17	0.093

Note: Analysis includes all observed rearrest events for each case. RA event number refers to the event sequence of rearrests.
Abbreviations: ApEn – approximate entropy; EMS – emergency medical services; RA – rearrest; Rhx – rhythm; RMSSD – root mean square of the successive differences; SD-HR – standard deviation of heart rate; VF/VT – ventricular fibrillation / ventricular tachycardia

6.8 FIGURES

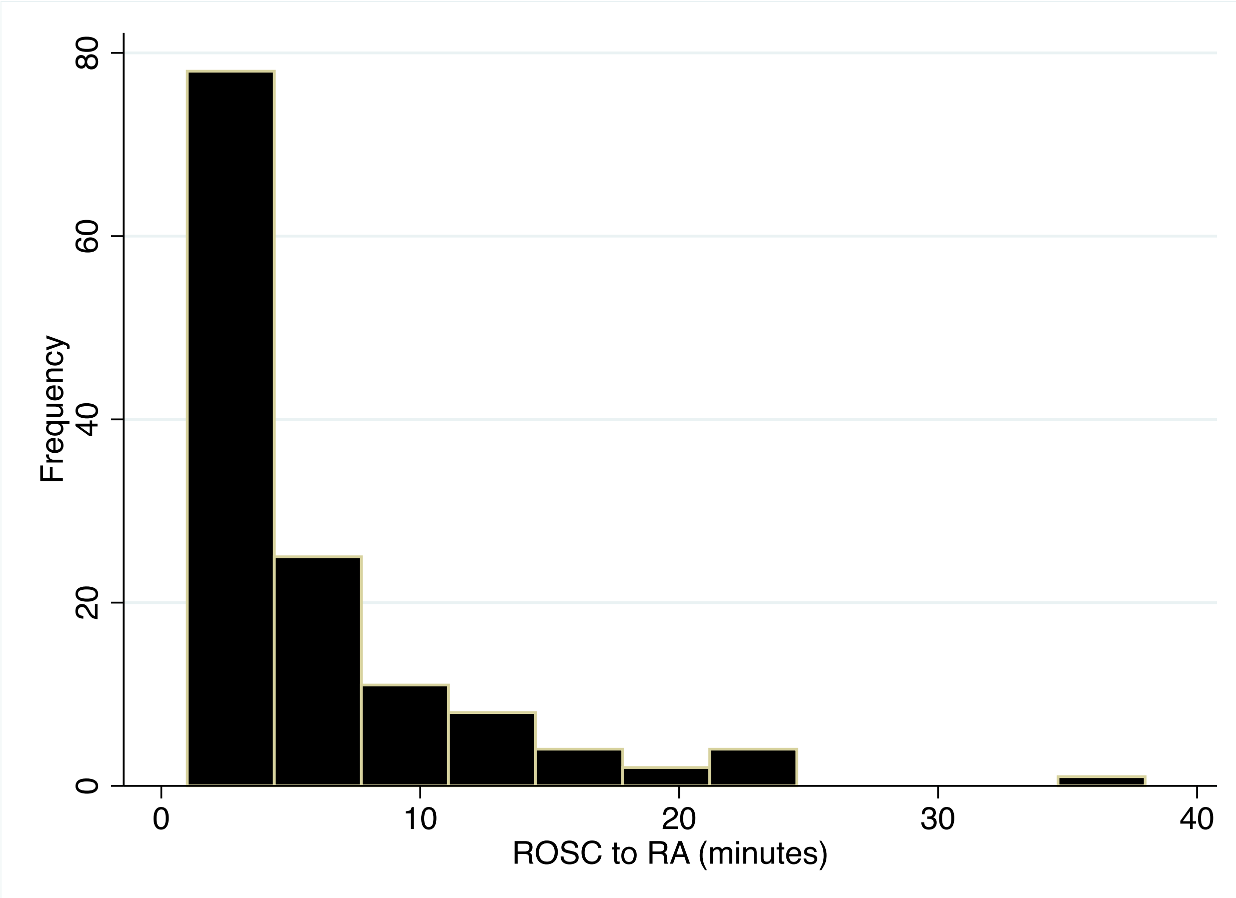

Figure 5. Histogram of All Available ROSC-to-Rearrest Intervals

Note: Frequency refers to the absolute count of events.

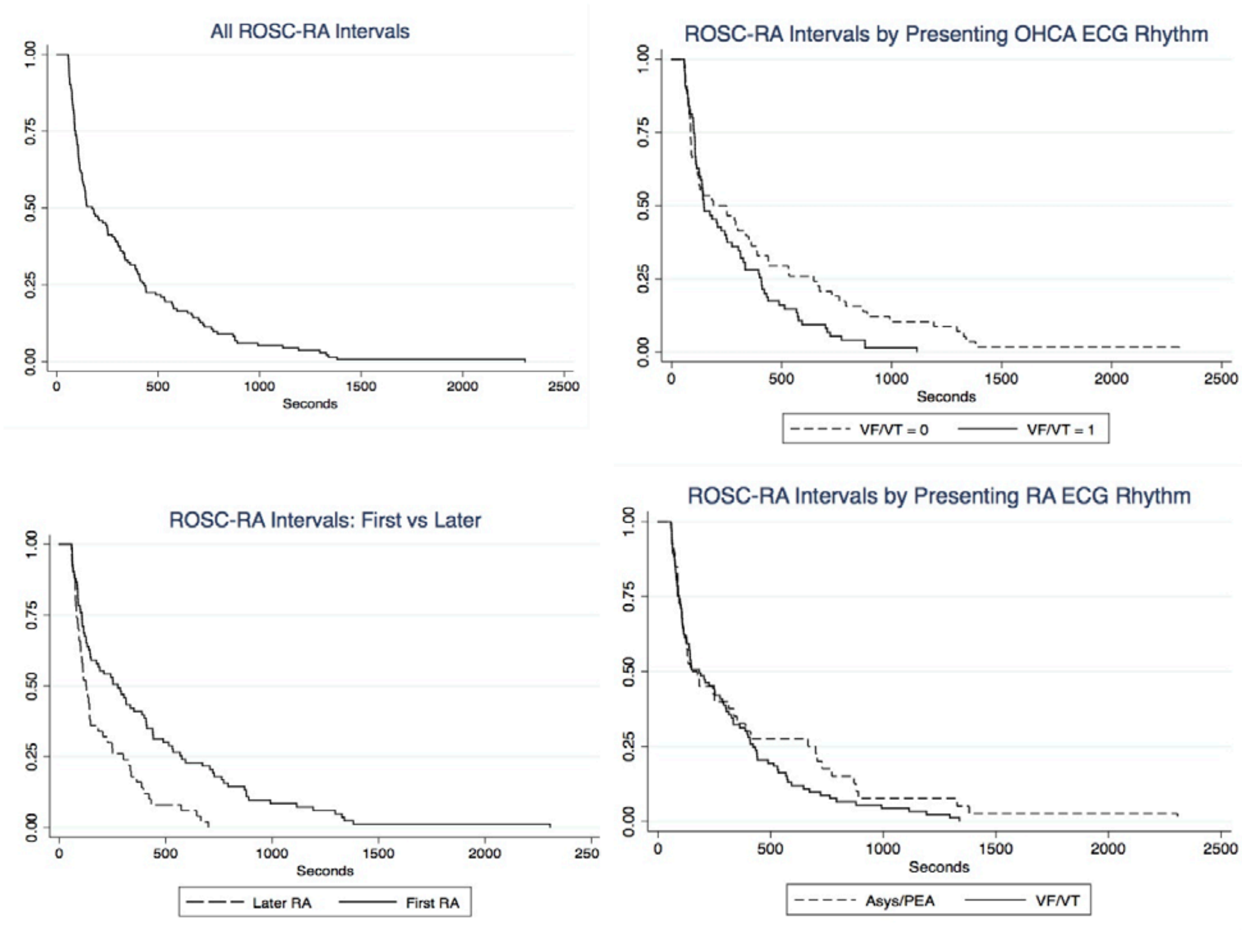

Figure 6. Kaplan-Meier Survival Curves from ROSC to Rearrest (Multi-Panel)

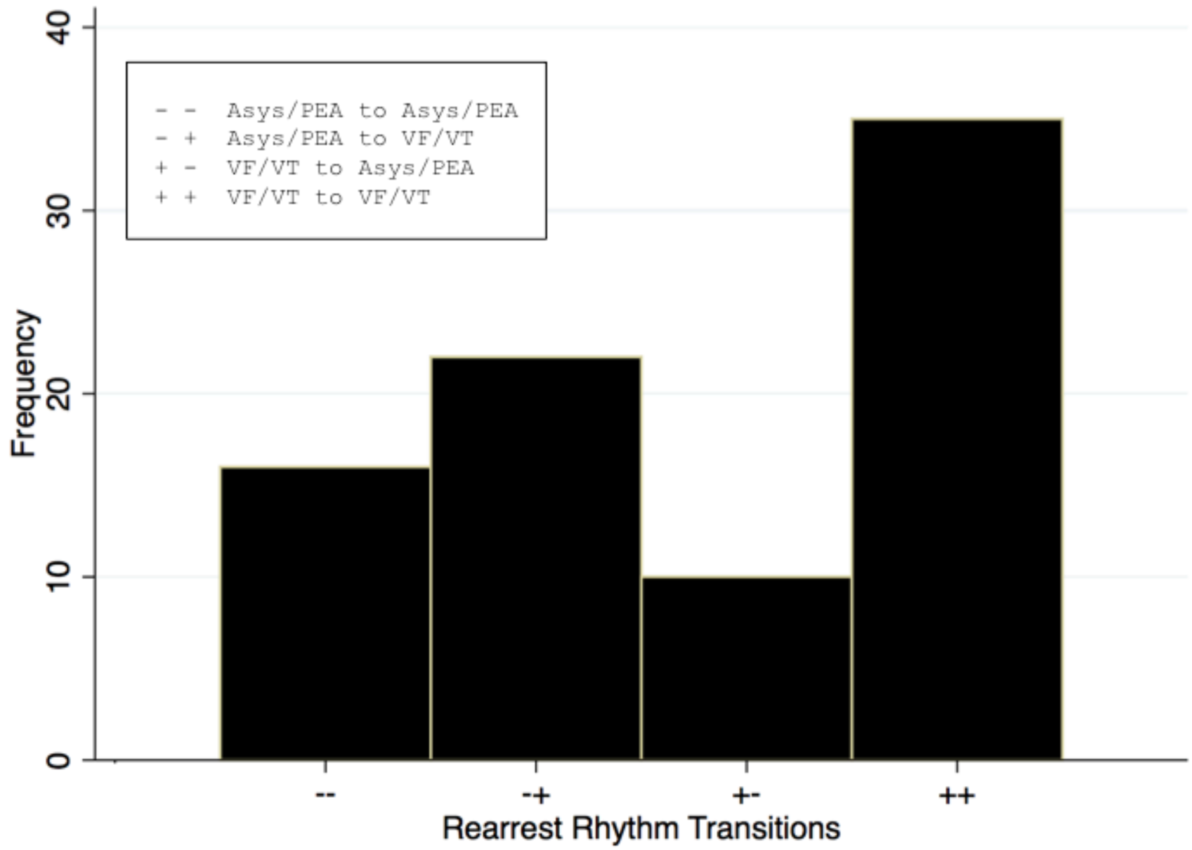

Figure 7. Pre-/Post-ROSC Secondary Rhythm Transitions

7.0 DISCUSSION

7.1 SUMMARY OF FINDINGS

The work presented in this dissertation embodies the first broad geographic description and likely the most in-depth analysis to-date of the phenomenon of rearrest following out-of-hospital cardiac arrest (OHCA). As such, it is necessarily an extension of the general body of literature concerning OHCA and resuscitation, and more broadly, the sequelae of chronic cardiovascular disease. In the continuum of this condition, rearrest lies sequentially between first exposure to risk factors for cardiovascular disease and post-cardiac arrest care in the intensive care unit or death. Between these bookends is a vast swath of causal and mediating events that for the resuscitation researcher intersect at the moment the heart stops beating. Rearrest may be an important downstream obstacle, and the present study provides information about the determinants and characteristics of rearrest that may aid in mitigating this obstacle.

Three general statements embody the principle findings of the present study:

1. *There are several case characteristics associated with rearrest.*
2. *Some characteristics, including some derived from the ECG, are associated with time-to-rearrest.*
3. *Certain characteristics are associated with the presentation of rearrest.*

These findings supplement work outlined in Appendix I, which established the incidence, mortality and geographic variability associated with rearrest. Taken together the findings of both studies provide a comprehensive introductory analysis of the phenomenon of rearrest, which is not without substantial limitations. Still, each finding has implications for the on-going aims of preventing, predicting, or treating rearrest.

7.1.1 Finding #1

In Paper 1, 3 classes of non-ECG-derived case characteristics were considered with respect to rearrest case status. In the final multivariable logistic regression model, 6 characteristics (and 2 procedural variables) were significantly associated with rearrest, at least one from each of the 3 classes of characteristics. Patient characteristics, time intervals, and drugs/treatments all showed some independent association with rearrest. However, the causal relationship between rearrest and some of these characteristics was ambiguous. It is unclear for instance, whether the increased probability of rearrest with atropine administration reflects an increased probability of downstream rearrest or the increased probability of downstream atropine administration after rearrest. Prior to 2010, atropine was recommended during asystole as a means of suppressing vagal input to the heart that may in turn be suppressing cardiac activity.[56] (It is no longer recommended for lack of evidence of effectiveness.) The proposed mechanism by which atropine acts to reverse asystole would seem to clash in part with the inference that atropine leads to rearrest. However, one could envision administration of atropine leading to ROSC and then creating favorable conditions for VF/VT rearrest.

In a sub-analysis within Paper 1, the field of characteristics was narrowed significantly to include only those that definitively occurred prior to rearrest and therefore could be considered predictors of rearrest, not consequences. Overlap between the first and second model included patient demographics, pre-ROSC time intervals, and OHCA condition variables such as presenting OHCA ECG rhythm, EMS-witnessed status, and public location. In this analysis, only median income (and the 2 procedural variables) was significantly associated with rearrest. For each increase in median income quartile, probability of rearrest relative to the first quartile increased by 14%. This relationship was robust to time-to-ROSC and time-to-CPR adjustment, suggesting that entanglement of socioeconomics with geographic scarcity of EMS resources was not necessarily responsible for the observed effect. What is unknown is whether the characteristics of agencies responding to OHCA in census tracts of given economic strata differ in practical ways that affect incidence of rearrest. Variation among the agencies included in this study has been described.[95] Moreover, median income of the census tract in which an OHCA occurs cannot intuitively be operationalized as a screening criterion for patients who may rearrest in the field. However, if this association were to hold up to further scrutiny, public health programs raising awareness of rearrest among EMS agencies might consider designing information dissemination programs around income-related parameters.

In Paper 2, the associations between a selection of ECG-derived characteristics and rearrest case status were examined. A limited number of characteristics derived from the QT-interval and sampled during the immediate post-ROSC period were associated with rearrest. The QT interval is reflective of the timing of depolarization and repolarization of the ventricles and can be prognostic of pathology.[86] In the prehospital setting, QT interval is normally considered through a 12-lead ECG recording.[56] By contrast, the present study makes use of non-traditional source data for QT-interval analysis, and considers both direct measurements of the QT-interval and an indirect approximation using the apex of the T-wave as the terminal end of the interval.[82] The latter method involves a compromise that offsets an underestimate of the QT-interval with a more reliable terminal landmark. The QT intervals observed in this study were close to the expected normal interval length of approximately 400ms in health individuals, lending some validity to the measurement approaches and source data employed.[96] However, no direct reference in the literature is available immediately after OHCA for comparison.

Between the two general classes of characteristics observed in this study - ECG and non-ECG – ECG characteristics are the only physiological measures and therefore the most directly connected to patient medical history prior to the OHCA. This relationship is complicated by the intervening OHCA and resuscitation, with metabolic derangement and drug administration potentially altering the ECG characteristics. Even so, diagnostic ECG analysis has been used to guide treatment following OHCA, including indication for percutaneous coronary interventions (PCI).[88] A greater understanding of the relationship between rearrest and existing pathology could provide a future basis for this kind of ECG-guided post-OHCA therapy.

7.1.2. Finding #2

In Paper 3, heart rate-derived ECG features were examined for associations with time-to-rearrest in cases that had identified rearrest events. Heart rate-derived features were chosen for their ready translatability to prehospital defibrillator/monitors. Considering 3 different analytical time frames, standard deviation of heart rate was inversely associated with time to rearrest when assessed on a 5-minute timescale. One-hundred millisecond increases in standard deviation resulted in more than a minute reduction in time-to-rearrest. Assessed in the 30-second and 1-minute timescale, presenting OHCA ECG rhythm and rearrest event number were inversely related to rearrest.

Time-to-rearrest event averaged 5.5 minutes for all rearrest events, although 49.6% of rearrest events were less than 3 minutes from the preceding ROSC event. The ability to anticipate an impending rearrest when the time-to-rearrest interval is shorter than 5 minutes is not robustly supported by the results of this study. Because time-to-rearrest intervals decreased after progressive rearrest events, the strongest indicator for anticipation of rearrest derived from this study may in fact be the previous occurrence of rearrest. One could suspect that shorter time-to-rearrest intervals may reflect deteriorating physiology, which might be evinced by a higher probability of Asystole/PEA type rearrest for shorter events. However, the association between rearrest event number and time-to-rearrest was observed independently of the ECG presentation of rearrest.

7.1.3. Finding #3

Paper 3 also examined factors associated with type of rearrest event. VF/VT first rearrest events tended to be more often experienced by males, while Asystole/PEA first rearrest events tended to be more often experienced by females. VF/VT first rearrests were nearly twice as likely as Aystole/PEA events to originate in VF/VT primary OHCA events. Lastly Asystole/PEA first rearrest events were much less likely to occur in cases with public locations of primary OHCA when compared to VF/VT.

Transitions between primary OHCA rhythm and subsequent rearrest rhythm were also considered. The most common transitions were stable transitions; that is, from a given primary OHCA rhythm to a rearrest of the same ECG presentation, although transitions from Asystole/PEA to VF/VT and VF/VT to Asystole/PEA were seen.

The significance of the ECG presentation of rearrest events for the prehospital healthcare provider lies in the treatability of the rearrest. Asystole/PEA essentially are only treatable with CPR, have generally poor outcomes as primary OHCA ECG presentations, and in the case of PEA specifically, carry the additional burden of being difficult to definitively determine.[56]

Whether it is worth anything to be able to predict the likelihood of the rearrest presentation independently of the time-to-rearrest or overall likelihood of rearrest is debatable. Coupled with the ability to accurately predict time-to-rearrest, however, prediction of the ECG presentation of rearrest would allow preparation of appropriate resources to treat the rearrest, assuming it is not entirely preventable.

7.2 CLINICAL SIGNIFICANCE OF REARREST

Central to the clinical significance of rearrest is the determination of whether rearrest is itself responsible for the negative outcomes with which it is associated, or if rearrest is simply reflective of pathology that results in poor outcomes. Equally important is the validity of the assumption that rearrest prior to hospital arrival stands apart mechanistically and prognostically from post-OHCA in-hospital cardiac arrest. A complete treatment of rearrest cannot avoid these questions, as they fundamentally determine the approach to treatment of rearrest.

7.2.1 Rearrest versus In-hospital Death

A critical philosophical and clinical aspect of this study is the operational definition of rearrest. The qualifier “operational” is critical when considering the implications and interpretations of this series of studies and any rearrest studies that come after it. For comparison, the term “cardiac arrest” implies a complete cessation of life sustaining cardiac output. OHCA is a qualification of this state that provides a location for the cardiac arrest event and carries the associated treatment limitations, prognoses, and epidemiology. “Rearrest” as applied in this study refers to an event downstream of an OHCA but prior to hospital admission. In this definition, the ostensibly arbitrary constraint of "prior to hospital admission" forces a distinction between patients who have a subsequent cardiac arrest event in the hospital from those who have one prior to OHCA. Why make this distinction? For the sake of this series of studies, the assumption was made a priori that in the absence of complete clinical data, including high-resolution temporal information about patient in-hospital condition, post-admission death could not be reliably attributed to the same causal mechanisms as those events that led to admission. Intuition says that the post-cardiac arrest ICU patient is not the same patient that had the antecedent OHCA. Profound neurologic dysfunction and multi-organ systems failure in the ICU might reasonably constitute a different milieu than the physiologic condition of the patient immediately after OHCA and resuscitation. In one of 4 elements of the clinical condition identified as Post-Cardiac Arrest Syndrome, ischemia-repurfusion injury due to the resuscitative process itself results in pathophysiological conditions that create morbidity that was not present when the patient initially experienced OHCA.[97] Additionally, one could argue that an in-hospital death due to a withdrawal of care, while justly constituting non-survival, would not be analogous to rearrest in the prehospital setting, although this is a very specific type of in-hospital death and inherently more distinguishable from others. However, this naturally leads into the consideration of treatments prior to rearrest, which differ greatly between the prehospital and in-hospital setting. The in-hospital patient who experiences a rearrest may be downstream of surgical manipulations or drug treatments that, while perhaps a consequence of the pathology underlying the initial OHCA event, are simply not present were that same patient to have rearrested prior to admission. In this sense, the prehospital rearrest event is almost exclusively a product of the extremity and etiology of the original OHCA event as well as the resuscitative interventions intended to mediate both, while the in-hospital rearrest event is a consequence of all of that, including any prehospital rearrests, mediated by any post-admission treatments and evolving morbidity.

7.2.2 Rearrest as Extremity

As alluded to, rearrest may provide a marker of the extremity of an OHCA if not directly contributing to survival. If this were the case, then one would expect rearrest to correlate with other markers of extremity. But what is extremity in a condition that results in temporary death for all patients and permanent death for the vast majority? The probability of survival to hospital discharge is one endpoint by which to gauge extremity when reflecting the effect of a given attribute of OHCA on prognosis of a group. Likewise, the probability of surviving with a given level of functional impairment and/or cognitive function can serve as case severity markers.[98] What in turn correlates with extremity or severity are those variables that influence these probabilities. As described in the introduction to this project, several factors correlate with the probability of survival and the loss or return of function, including initial ECG rhythm, initial downtime, age, witness status, and etiology of OHCA. In the present study, rearrest did correlate inversely with VF/VT initial rhythm, which supports the extremity argument. However, rearrest was also inversely correlated with time to first ROSC event, which suggests the opposite. This finding is not entirely surprising however, as it is easy to lose track of the fact that unlike most other OHCA studies, in this series of studies ROSC was a necessary inclusion criterion. This could potentially have removed much of the acute prognostic explanatory power of time to first ROSC. While the association between rearrest and survival may present the most convincing argument of its utility as a marker of extremity, a better marker might be neurologic or functional outcome, neither of which were ascertainable in this dataset. Supposing that either were available, one would expect that rearrest would correlate directly with post-resuscitation neurologic and functional impairment.

7.2.3 Rearrest as Insult

Were rearrest to be causally related to worsened outcomes after OHCA, one could posit three plausible general mechanisms. In the first, rearrest could add to total no-flow and low-flow (i.e. CPR) time for any case in which it occurs at least once. For cases of equal characteristics, including no-flow and low-flow time, in all other senses except the occurrence of rearrest, one would expect equivalent outcomes on average. This hypothetical mechanism does not rule out the proposition that rearrest is a marker of case severity, and in fact may be simply recursive process inflicting insult upon pre-existing injury. In the second mechanism, the process of resuscitation may be deleterious to the patient when repeated for more than one arrest event. The effects of repeated electrical defibrillation, prolonged chest compression, and repeated administration of vasoconstrictive drugs might contribute to poor outcomes under the right conditions. The process of establishing how these treatments interact with time and existing pathology to lead to worsened outcomes might be impossible in an observational study however. Lastly, in the third mechanism, rearrest may perturb the behavior of health care providers, leading to suboptimal performance following a rearrest. In this scenario, the low-flow time during the treatment of rearrest would be expected to be more deleterious than the low-flow time during the primary OHCA event. For cases of equal CPR treatment time but no rearrest event, one would then expect better CPR performance parameters on average, better perfusion during equivalent low-flow time, and therefore better outcomes on average. It is important to note that the 3 mechanisms speculated upon here are not necessarily mutually exclusive, and the present study does not give any reason to believe that all three mechanisms are not at work.

7.3 LIMITATIONS

The major limitations of the present study derive from the context in which the study was conducted; that was a secondary analysis of data (acquired, cleaned, analyzed and presented by the author) collected as part of a large, multi-site OHCA clinical research network, the Resuscitation Outcomes Consortium. In order to understand the implications of this design, some context is necessary.

ROC OHCA surveillance is conducted through partnerships with local EMS agencies within the service areas of participating clinical sites.[99] Surveillance mechanisms include active and passive components, although specific implementation varies between sites. Furthermore, data collection follows an established architecture developed by consensus and updated periodically, known as the ROC-Epistry, a contraction of the terms "epidemiologic" and "registry." The data fields dictated by the Epistry draw from prehospital patient care reports, defibrillator-derived records, computer aided dispatch records, hospital records, and miscellaneous related sources. By design, the Epistry includes hundreds of data fields describing the patient, provider, treatments, and circumstantial conditions surrounding each episode of OHCA. While this complement of data is intended to be comprehensive in any given version, it presents a limit for future studies that engage subjects outside the scope of the version of the Epistry when each case was captured.

The present studies were conducted with data derived from a specific time period, 2006 to 2008, within the on-going surveillance activity of the ROC-Epistry. This period was chosen by elimination, as at the time that the study was initiated, surveillance activities of the Epistry were diverted toward the on-going early clinical trials mentioned above, collectively referred to as the PRIMED trial, and all contemporary surveillance data were embargoed.[100] Any findings from the present study faces limits of generalization beyond the period of 2006-2008, in particular beyond the year 2010, when AHA/ILCOR guidelines for treatment of OHCA were updated. Changes at that time included a prioritization of chest compressions over airway checks and ventilation, and a recommendation to prioritize drug delivery over advanced airway placement.[56]

Rearrest, as investigated in this series of studies, is a relatively novel resuscitation clinical endpoint. As described in the overview to this document, there is even now very little in the way of all-rhythm rearrest literature, and even refibrillation and recurrent ventricular fibrillation in the out-of-hospital setting were relatively under-studied at the inception of the ROC. It is not surprising then that the ROC-Epistry as originally constructed did not directly include a rearrest ascertainment variable. As demonstrated in the methods described above, this limitation did not make rearrest ascertainment impossible, however it necessitated two general coping strategies. In the first, data points were identified within the intact ROC-Epistry that could be used to draw inference about rearrest occurrence when viewed in the context of other variables or general constraints of the data set. In the second, signal data not directly incorporated into the Epistry were used to supplement the existing data. The latter strategy was decidedly a strength of this study rather than a weakness. However as mentioned before, the former source was the predominant source of ascertainment data and likely resulted in an artificially low estimate of rearrest incidence and likely an increased association with markers of difficult resuscitation.

Reliance on these data also presented a number of other limitations that leave open possibilities for future studies, to be expounded upon in the next section. Among these were the lack of patient medical history, the inability to speculate directly about regional incidence or survival rates due to site blinding requirements, only cursory information about the timing of prehospital treatments, no information about in-hospital treatments, and no long-term follow up of patients who survived to hospital discharge. In the story of rearrest as an event between the bookends of exposure to cardiovascular risk factors and survival beyond hospital discharge made at the beginning of this section, both the beginning and the end of the story are lost in the embodiment of the data available for this study.

7.4 FUTURE WORK

The present studies have left many unanswered questions that merit follow-up in future projects.

The vast majority of case data utilized in this study comprised pre-abstracted data, derived from no-longer-available signals and written medical records, greatly constraining estimates of rearrest incidence and analyses of rearrest signal characteristics. The data infrastructure whence these data were derived is now mature and highly efficient, capturing by recent internal estimates up to 75% of available defibrillator signals. Rearrest surveillance with data collected after the primary data of the present study can take advantage of this increased capture in order to make additional, more sensitive estimates of rearrest incidence.

Increased data availability and the fact that the major surveillance infrastructure of the ROC is now nearly 10 years old also contribute to the investigation of temporal trends in rearrest incidence, an expansion of the present studies' aims. AHA/ILCOR guidelines for OHCA treatment are updated every 5 years to reflect evidence accumulated through on-going resuscitation research. The present study does not provide sufficient temporal scope to examine the relationship between changes in treatment guidelines, or simply secular trends in population characteristics, and incidence, outcomes or characteristics of rearrest cases.

Why rearrests occur in some patients but not others remains to be established. The present studies demonstrated that some patient and treatment characteristics correlate with rearrest status, but the causality of these relationships remains ambiguous. A major aim of future studies would be to understand how temporally variant characteristics such as drug administration relate to rearrest events. Epinephrine, for instance, is associated with rearrest and with "difficult" resuscitations. Properly designed prospective studies would include time stamp information for each epinephrine administration so that they could be localized with respect to the each rearrest event.

The present study also did not include detailed patient history, so direct inference as to the underlying mechanisms of the primary cardiac arrest event, let alone subsequent rearrests is impossible. Future studies can be designed to use detailed review of critical elements of patient medical records, both before and after the primary OHCA to determine underlying pathology.

At least one form of rearrest, that presenting as VF/VT, may have a direct pharmacological intervention available within the arsenal of current medical treatments that could provide the basis for a near-term clinical trial. As two studies have already shown, antiarrhythmics can be utilized by paramedics to increase survival in patients who do not respond to standard resuscitation measures.[57-58] If we suppose that the general mechanism of action of amiodarone in these studies was to decrease the likelihood of rearrest once pulses were successfully restored, then protocolization of antiarrhythmic administration for patients with rearrest may be logical. There is of course the question of whether antiarrhythmic should be administered intra-arrest as was the case in the aforementioned studies, or if these drugs could or should be administered immediately after ROSC.

Lastly, at this moment the study of rearrest is currently limited to human clinical data, which presents significant constraints on the experimental range of studies. An animal model of rearrest, while not contributing directly to the epidemiologic understanding of rearrest, may provide a basis for testing hypothetical mechanisms for rearrest and its prevention. Findings in this model could then be formulated into aims for clinical studies.

7.5 PUBLIC HEALTH IMPLICATIONS

As described previously, the public health burden of OHCA is enormous. While incidence of OHCA varies between geographic regions, it is serious public health problem throughout the developed world. OHCA has a high case fatality rate, and morbidities related to OHCA, including functional and cognitive deficits in survivors are common, requiring substantial rehabilitation. Survivors of OHCA often are discharged to long term assisted living facilities and some may never return to their pre-OHCA level of independence.

Considering how rearrest fits into the overall picture of OHCA helps to frame this sub-condition as it relates to the public at large and is illustrative to how this study is rooted critically in the interest of public health. Given that nearly 350,000 OHCA occur in the United States each year[4], and noting that approximately 140,000 (40%) of these cases will regain pulses in the course of EMS treatment, we can calculate conservatively that at least 24,500 cases experienced rearrest.

Public health initiatives to reduce the burden of OHCA have been attempted over the past 60 years with varying degrees of success. The most prominent of these could be the modern EMS system, providing rapid identification and treatment for OHCA within minutes of dispatch over wide geographic areas. Protocolized care for OHCA by EMS emerged from the realization that minimizing time to treatment is critical for survival. In the United States and much of the developed world, EMS of some kind is ubiquitous, and care for OHCA patients is guided by treatment protocols that defer to evidence-based guidelines issued by organizations like the AHA and ILCOR. These efforts have been followed by the introduction of layperson CPR training and public access defibrillation programs.[101,102] Both initiatives are generally aimed at closing the gap between recognition of an OHCA and onset of treatment. Both layperson, or *bystander*, CPR and public access defibrillation depend on dissemination of knowledge and willingness to act. As such, participation in either program varies greatly between populations, as does effectiveness.

It is critical to note that the high case fatality and morbidity rates for OHCA exist in spite of the major public health efforts mounted against it. From a practical standpoint, these efforts are designed to restart the heart, but this is only one part of ensuring survival from OHCA. There is unfortunately a large degree of overlap between the time often required to restart the heart and the amount of downtime necessary to develop irreversible brain damage.

In the present study, rearrest was found to substantially increase the risk of death prior to hospital discharge. This finding provides insight into understanding the factors that contribute to death after OHCA despite public health efforts, evidence based treatment guidelines, and intensive in-hospital care. This finding alone provides a potential target for modification of current in- and out- of-hospital OHCA treatment protocols to accommodate a factor that has been shown to relate not to simply restarting the heart, but to survival. The most logical step may be to encourage rapid, efficient transport to hospital during treatment of the primary OHCA. All other things being equal, closing the time between the initial ROSC event and hospital admission could obviate many rearrest events.

APPENDIX A: PRECURSOR PAPER – INCIDENCE AND OUTCOMES OF REARREST

Incidence and Outcomes of Rearrest Following Out-of-Hospital Cardiac Arrest

Salcido, Incidence and Survival After Rearrest

Submitted for publication and currently under review

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Abstract

Background: Rearrest (RA) occurs when a patient experiences cardiac arrest after successfully achieving return of spontaneous circulation (ROSC). The incidence and outcomes of RA following out-of-hospital cardiac arrest (OHCA) have been estimated in limited local studies. We sought to investigate the incidence and outcomes of RA over a broad geographic area.

Methods: This retrospective study was approved by the University of Pittsburgh Institutional Review Board. We obtained case data from EMS-treated, non-traumatic OHCA from the Resuscitation Outcomes Consortium, a multi-site clinical research network conducting population level surveillance of OHCA in 11 cities in the US and Canada. The study cohort comprised all OHCA cases surveilled between 2006 and 2008 at ROC sites and having prehospital ROSC. We used three methods to ascertain RA incidence among these cases: direct signal analysis, indirect cardiopulmonary resuscitation (CPR) process analysis, and emergency department arrival vital status. RA incidence was estimated as the proportion of cases with ROSC that experience RA, and survival was calculated as the proportion of patients with ROSC surviving to hospital discharge. Regional RA estimates were compared with the Chi-Squared test. Multivariable logistic regression was used to assess the relationship between RA and survival to hospital discharge.

Results: Out of 18,937 cases of EMS-assessed OHCA captured between 2006 and 2008, 11,456 (60.5%) cases were treated by EMS and 4,396 (38.4%) had prehospital ROSC. Of these, sufficient data were available for RA ascertainment in 3,253 cases, with 568 (17.5%)

experiencing RA. Regional RA incidence varied significantly from 10.2% to 21.2% ($p < 0.001$). RA was significantly inversely associated with survival (OR: 0.19, 95%CI: 0.14 – 0.26).

Conclusions: In this geographically broad and inferentially conservative analysis, RA occurred on average in 1 of every 6 successfully resuscitated patients, though incidence varied significantly across 10 sites in North America. RA was inversely related to survival to hospital discharge.

Keywords: Cardiac Arrest, Resuscitation, Emergency Medicine, Electrocardiography

Introduction

Rearrest (RA) is one potential stumbling block in the pathway to survival for the out-of-hospital cardiac arrest (OHCA) patient. RA occurs when a resuscitated patient experiences a subsequent cardiac arrest. Contextualized to OHCA, the term RA generally applies to the short term, covering the time period from first resuscitation to hospital admission. As a condition classification, RA captures cardiac arrest of all electrocardiogram (ECG) presentations, distinguishing itself from *refibrillation*, with an ECG presentation of ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), by encompassing that condition as well as cardiac arrests presenting in pulseless electrical activity (PEA) and asystole, the classic flat-line ECG trace. Estimates of the incidence of RA among patients with ROSC run as high as 79% when considering studies that only looked at refibrillation.[1-6] However, most such studies used a defibrillation success criterion of "non-VF post-shock rhythm," blurring the distinction between RA as a loss of pulses and RA as a transition between cardiac arrest ECG rhythms. In the few studies that have considered all-rhythm RA, RA incidence estimates ranged from 5% to 39%.[7-10] Of critical interest, a number of studies in both categories have indicated that RA can be detrimental for patient survival, although the mechanism for this association remains unclear. [3,6,9]

While the ultimate goal in investigating rearrest would be to prevent it through an understanding of its causes, the first step in this process is to understand the epidemiology of rearrest and the general relationship of rearrest to survival. In the present study, we provide descriptive epidemiologic characterization of rearrest using data from multiple cities in North America. Although the primary aim of this study was description, we also began with a hypothesis, namely that the incidence and outcomes of rearrest would vary regionally, just as OHCA and survival after OHCA have been found to vary regionally.[11]

Methods

The University of Pittsburgh Institutional Review Board approved this retrospective cross-sectional study. Case data were obtained from the Resuscitation Outcomes Consortium (ROC), a North American research network studying cardiac arrest and severe trauma in 11 US and Canadian cities, however all study analyses were conducted at the University of Pittsburgh. One of the primary aims of the ROC is to maintain an active surveillance program for OHCA, where cases are identified and captured at the emergency medical services (EMS) level with in-hospital follow up for outcomes assessment. For the purpose of this study, case data were obtained only for non-traumatic OHCA cases receiving some treatment from EMS. This eliminated cases that were presumed dead on arrival of EMS.

An additional inclusion criterion was any prehospital return of spontaneous circulation (ROSC), a necessary precursor to RA. All case data were derived from OHCA events occurring in a fixed study period running from early January 2006 to December 2008, and came from 10 of the 11 ROC sites, with 1 site contributing no data during this time period. The study period corresponded to the post- ramp up phase of the ROC surveillance infrastructure and ended at the initiation of a ROC-wide clinical trial, which resulted in changes to resuscitation protocols at participating sites and a data embargo.

Data fields collected for each case by the ROC included a panel of variables capturing patient characteristics and outcomes, treatments, event order and timing, provider characteristics, and process measures. Data were abstracted by ROC research specialists from prehospital patient care reports, electronic defibrillator downloads, and hospital medical records and were made available to us as a single de-identified database. In addition, we were also given access to original electronic defibrillator downloads for cases when they were available.

RA was ascertained in this study by three distinct methods. Three methods were used in order to maximize ascertainment in the absence of completed data fields, the breadth of which we describe in detail in the presentation of our results. In short, prior to our study, ascertainment of RA was not a priority of the ROC, so our retrospective investigation relied upon inference through available data. Figure 1 provides a visual synopsis of the detailed methodologies described below.

RA Method 1

The first RA ascertainment method was the direct analysis of continuous defibrillator download data streams. While data stream content was manufacturer-dependent, defibrillator files available to us contained at a bare minimum continuous ECG and transthoracic impedance, a common signal modality used to detect chest compressions in resuscitation case review. Other signal modalities were often but not always present, and included end-tidal carbon dioxide, chest compression depth from sternal accelerometry, and chest compression force from a sternal strain gauge. When defibrillator downloads were available, we reviewed their content for evidence of rearrest, where signal-ascertained rearrest was defined as at least 1 minute of the patient lacking a pulse post-ROSC, as evinced by obvious lethal arrhythmia in the ECG trace, chest compressions in any available chest compression reference data stream, or audible declaration of loss of pulses by paramedics in the audio data stream. In this method, ROSC was defined as 1 minute of pulses, evinced by absence of chest compressions, non-lethal ECG rhythm, and, if present, audible paramedic confirmation of pulses.

RA Method 2

The second RA ascertainment method involved the indirect analysis of defibrillator download data by way of previously extracted process metrics. In this way, even though a complete defibrillator download signal for a given case was not available, abstracted time-series data from the case could still be analyzed. During the 2006-2008 study period, ROC data abstractors had routinely tabulated cardiopulmonary resuscitation (CPR) process parameters throughout the first 20 available minutes of resuscitation. Process parameters were collected from electronic defibrillator downloads, which were analyzed but not retained, as minute-by-minute averages of chest compression rate and chest compression fraction, as well as raw chest compression count. Minute-by-minute process parameters were accompanied by qualifying variables indicating the reason for absence of parameters, if absent, at any of the 20 potential measurement time points. Included in this field was a value specifying that no parameters were recorded during a time point due to ROSC. Systematically analyzing the CPR process parameters over time with a custom MATLAB program (Mathworks R2011a, Nattick, MA), we first identified gaps in CPR. We could then infer to the presence of ROSC either by direct reference to the qualifying data field or through a time criterion. In the latter case, we separately considered periods of 1, 2, and 3 minutes without chest compressions as ROSC. Both methods were considered in separate analyses within this study. RA could then be ascertained as the resumption of CPR following a ROSC-identified gap in the CPR process parameter timeline for a given case.

RA Method 3

The third method was the assessment of a distinct, limited category of RA based on the presence or absence of pulses upon the patient's arrival at the hospital. Each case in our study cohort was identified as having ROSC prior to hospital arrival. Separately, ROC data abstractors identified patient vital status at emergency department (ED) arrival. It follows that any patient arriving at the ED without pulses had undergone RA at some point between achieving ROSC in the field and ED arrival.

Combined RA Estimate

In order to produce an estimate of RA incorporating the maximum number of cases for which data were available, we created a conservative, composite RA variable incorporating data from each of the 3 methods. RA status for each case was taken from one of the 3 methods, using the prioritization scheme illustrated in Figure 1. In this way, direct signal analysis received the highest priority, while ED vital status received lowest. To produce the composite estimate, we erred on the sides of under-estimation and accuracy by only using Method 2 with annotated ROSC for the final overall analyses.

Analyses

Total RA incidence over the study period was estimated as the proportion of cases with RA out of all cases with available RA ascertainment data fields. Sub-estimates of incidence were also estimated for each method independently. Incidence estimates and other proportions were compared with the X^2 test. Logistic regression was used to assess the relationship between RA and the outcome of survival to hospital discharge. Multivariable regression models were constructed for both analyses and included age, sex, witness status, presenting cardiac arrest rhythm, and consortium site. In both multivariable models, the site coded ‘J’ was selected automatically by our statistical software as the reference site. All statistical analyses were conducted with Stata 12 (StataCorp, College Station, TX) with an alpha of 0.05

Results

A total of 18,937 cases of EMS-assessed OHCA were detected by the ROC during the study period spanning 2006-2008. Of these, 11,456 (60.5%, 95%CI: 59.8-61.1) cases were treated by EMS, and a further subset of 4,396 (38.4%, 95%CI: 37.5-39.3) cases were found to have a detectible prehospital ROSC event, forming the basis of our study cohort. Table 1 gives a summary of basic case characteristics for the overall study cohort.

Defibrillator download files (Method 1) were directly available to us for 370 (8.4%) cases from the study cohort, 20-minute CPR process data (Method 2) were available for 1,222 (27.8%) cases, and ROSC at ED arrival (Method 3) was available for 2,913 (66.3%) cases. At least one RA ascertainment variable was available for a total of 3,253 cases, or 74% of the study cohort, with 52.5% of cases having only one variable available, 14.5% having 2, and only 6.8% having all 3 variables available. Individual and combined RA incidence estimates are reported below and summarized in Table 2, along with odds rations for survival when each method of RA ascertainment represented RA status in separate multivariable logistic regression models.

Method 1 Estimate

Of the 370 signals available to us, 294 (79.5%) were analyzable. Seventy-six signals either lacked a clear occurrence of ROSC, presented unusual ECG wherein lethal arrhythmia could not be ruled in or out, or lacked a CPR reference data stream by which to determine the cessation or resumption of chest compressions. Of those cases that were analyzable, RA was present in 113, yielding an RA incidence by direct signal analysis of 38.4%. Cases in this subset experienced, on average 1.6 (1.2) RA events (median: 1, IQR: 1-2) over a total of 4,929 minutes of signal analyzed. The mean (SD) time to first RA was 6.6 (6.5) minutes from ROSC, with a median of 4.4 (1.8-9.3).

Method 2 Estimate

Estimating RA incidence with an interpretation of 1 minute of no CPR as ROSC resulted in a CPR process based incidence estimate of 16.1%. Estimating RA incidence conservatively for cases with available ROSC annotation data resulted in CPR process based incidence estimate of 2.3%. In these cases, bearing in mind that the data source imposed a twenty-minute ascertainment period limitation on our analyses, the average number of RA per case was 1.1 (0.4) (median: 1, range: 1-2) events over a total of 9,133 minutes of CPR process data. The mean (SD) time to first RA was 3.5 (2.8) minutes from ROSC, with a median (IQR) of 3 (1-5) minutes.

Method 3 Estimate

Of 2,913 cases with a valid ROSC at ED arrival variable, 16.7% of cases qualified as RA. This method of classification of RA alone does not allow for the determination of number of RA events or relevant time intervals (e.g. when RA occurred).

Combined Estimate and Models

Allowing for any of the 3 methods of ascertaining RA and restricting Method 2 ascertainment to definite ROSC (Method 2.4), 568 cases (17.5%) out of 3,253 cases with RA data experienced at least one RA event. Over the 10 sites, incidence of RA varied significantly from 10.2% to 21.2% ($p = 0.01$). Stratified by presenting cardiac arrest ECG rhythm, rates of RA did not differ significantly ($p = 0.48$); see Figure 2. In a univariate model, RA was significantly predictive of survival to hospital discharge (OR: 0.25, 95%CI: 0.19 – 0.34). The effect remained in a multivariable model adjusting for age, sex, presenting ECG rhythm VF/VT, EMS witness status, bystander resuscitation, and public/private location of OHCA (OR: 0.19, 95%CI: 0.14 – 0.26). Results of the regression analysis are shown in Table 3.

Discussion

Our principle finding is a general estimate of RA incidence. Overall, by way of our most conservative estimation scheme, we found that RA occurred in 17.5% of OHCA cases achieving ROSC. The selection process for our study cohort yielded an overall consortium rate of ROSC at 38.4%. Thus it follows that only 6.7% of EMS-treated OHCA patients experience RA. This figure is deceptively small, given that in the nearly 62% of patients who never regain pulses during resuscitation, RA is impossible and therefore clinically irrelevant. Still in comparison to previous single-site studies, our overall RA rate estimate is low. In single-city analyses, both our group working in Pittsburgh and Lerner et al. working in Milwaukee found local RA rates approaching 40%.[8,9] However, it should be noted that our estimate of RA by Method 1 – 38.4% - was in very close agreement with these previous estimates. When we considered cases with presenting ECG rhythm of VF/VT alone, overall RA rate was not radically different from our all-rhythm estimate, but differed from estimates of *refibrillation* in previous studies[1-5].

Also of significant interest, we found that RA was inversely predictive of survival. While this finding is intuitive and supports previous studies – though not explicitly reported, the OR for survival with RA versus No RA cases in the study by Lerner et al. was approximately 0.3 – the specific relationship between RA and survival is not clear. Patients with RA were significantly less likely than patients without RA to have a witnessed OHCA or a presenting ECG rhythm of VF/VT. This finding may provide further insight into the challenges of resuscitating initially non-shockable OHCA ECG rhythms.

We provide a broad geographic analysis of RA incidence. RA rates differed significantly across the 10 participating consortium sites, mirroring previously established diversity in OHCA incidence and survival rates across the same areas.[11] We do not disclose site identity in this paper, out of agreement with the ROC, so we cannot explicitly assess the relationship between these past site-specific estimates and our current RA estimates. However, factors that influence both rates may also be instrumental in RA incidence and outcome, so further detailed analysis is necessary and forthcoming.

Our study offers a new classification of RA, RA determined solely by ED vital status, which we call unresolved prehospital RA (UP-RA). While UP-RA is the most informationally limited measure of RA available from our data set, it provides strong predictive power for negative outcomes after OHCA. The relationship between UP-RA and poor outcomes could be useful with a full understanding of its determinants, characteristics, and consequences. Further characterization of this phenomenon is necessary.

We provide two estimates of mean time-to-RA in this study of 3.5 and 6.6 minutes by direct and indirect signal analysis. These times compare closely to our previous single-site estimate of 3.1 minutes.[8] Time intervals between ROSC and RA of this magnitude provide a potential therapeutic window for preventing RA before it happens, with the caveat that such interventions are most likely to be necessary in the prehospital environment with all of the constraints and conditions that it carries.

Our study has several limitations related primarily to the retrospective data that formed the basis of our investigation. Due to several infrastructure issues outlined in our methods, we could not directly analyze the raw resuscitation signal for many of the cases in our cohort. This necessitated the adoption of alternative methods of rearrest ascertainment that indirectly inferred to the loss of pulses after ROSC. Both alternative methods are conservative, biasing ascertainment toward a non-event. Even so, all three methods – including Method 2.1 of indirect signal analysis – were independently predictive of survival in multivariable models, indicating some validity by effect equivalence. With respect to outcomes, we were unable to specifically investigate the in-hospital contributors to the survival or death of subjects in our cohort, including therapies, co-morbidities, secondary conditions, and indeed actual cause of death. Additionally, we did not have access to neurologic outcome data for our cohort, leaving open the possibility that RA, though inversely associated with survival, may or may not impact neurologic status at hospital discharge. Lastly, we derived our conclusions from data spanning a relatively narrow 2-year surveillance period ending 5 years ago, leading to the possibility that both the temporal scope and the detachment from changes that have occurred since then may limit generalization of our findings.

Conclusion

In this geographically broad and inferentially conservative analysis, RA occurred on average in 1 of every 6 successfully resuscitated patients, though incidence varied significantly across 10 cities in North America. RA was inversely related to survival to hospital discharge.

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FIGURE LEGEND

TABLES

Table 12A. Cohort Characteristics by Site

ROC Site	Age, Years, Mean(SD)	Male, %(95%CI)	Public Location, %(95%CI)	VFVT Presenting Rhx, %(95%CI)	EMS Witnessed, %(95%CI)	Bystander Resuscitation %(95%CI)	Survival %(95%CI)
A	**62.2(16.6)**	**63.9(59.5-68.2)**	**22.9(19.1-26.7)**	**42.9(38.4-47.4)**	**5.3(3.3-7.3)**	**60.9(55.7-66.0)**	**29.0(24.8-33.2)**
B	**62.3(16.5)**	**64.7(61.4-68.0)**	**25.3(22.3-28.3)**	**39.7(36.2-43.1)**	**14.7(12.3-17.2)**	**48.6(45.2-52.1)**	**35.4(31.9-38.8)**
C	**65.6(16.2)**	**62.4(58.6-66.2)**	**17.1(14.2-20.1)**	**40.3(36.4-44.2)**	**16.2(13.3-19.0)**	**31.0(27.3-34.6)**	**20.9(17.6-24.1)**
D	**60.4(15.2)**	**46.2(30.3-62.0)**	**15.8(4.0-27.5)**	**38.9(22.7-55.0)**	**12.8(2.2-23.5)**	**57.7(38.3-77.1)**	**12.9(0.9-24.9)**
E	**61.6(19.5)**	**65.9(59.3-72.4)**	**22.9(17.2-28.7)**	**43.6(36.5-50.7)**	**18.5(13.2-23.9)**	**39.1(31.8-46.4)**	**41.0(34.1-47.9)**
F	**63.9(16.8)**	**68.4(65.5-71.4)**	**25.2(22.5-28.0)**	**46.9(43.7-50.1)**	**12.2(10.1-14.3)**	**39.8(36.7-42.9)**	**25.1(22.1-28.0)**
G	**61.1(19.2)**	**50.4(44.2-56.6)**	**16.1(11.6-20.7)**	**24.9(19.5-30.3)**	**15.0(10.6-19.4)**	**26.0(20.6-31.4)**	**26.4(20.8-32.0)**
H	**64.9(16.4)**	**52.9(45.8-59.9)**	**16.6(11.3-21.8)**	**31.1(24.5-37.7)**	**8.8(4.8-12.8)**	**49.4(42.1-56.8)**	**29.7(23.1-36.3)**
I	**61.6(16.4)**	**61.0(51.6-70.3)**	**13.3(6.8-19.9)**	**43.2(32.4-54.1)**	**10.5(4.6-16.4)**	**47.2(33.6-60.7)**	**27.5(18.2-36.7)**
J	**67.0(16.1)**	**61.7(58.2-65.2)**	**18.7(15.8-21.5)**	**36.0(32.5-39.5)**	**15.8(13.2-18.5)**	**33.2(29.8-36.7)**	**25.0(21.8-28.3)**
Overall	**63.9(16.9)**	**63.0(61.6-64.5)**	**21.4(20.1-22.6)**	**40.1(38.6-41.5)**	**13.4(12.3-14.4)**	**40.6(39.1-42.1)**	**27.8(26.4-29.2)**

Abbreviations: ROC – Resuscitation Outcomes Consortium, VFVT – Ventricular Fibrillation / Ventricular Tachycardia, CI – Confidence Interval, SD – Standard Deviation, Rhx – Rhythm.

Table 13A. Rearrest Incidence by Method - Summary

Rearrest Ascertainment Method	Analyzable Cases n	Rearrest Rate % (95%CI)	Survival Adjusted* OR (95%CI)
Method 1 – Direct Signal Analysis	294	38.4 (32.8-44.0)	0.45 (0.22-0.90) #
Method 2.1 – CPR Process (ROSC = 1 min)	1,222	16.1 (14.1-18.2)	0.50 (0.32-0.79) #
Method 2.2 - CPR Process (ROSC = 2 min)	1,222	6.5 (5.2-7.9)	0.66 (0.34-1.28)
Method 2.3 – CPR Process (ROSC = 3 min)	1,222	4.5 (3.3-5.7)	0.61 (0.27-1.37)
Method 2.4 – CPR Process (annotated ROSC)	1,222	2.3 (1.5-3.1)	1.20 (0.46-3.12)
Method 3 – ED Vital Status	2,913	16.7 (15.3-18.0)	0.14 (0.01-0.20) #
Combined RA with Method 2.1	3,253	18.6 (17.3-20.0)	0.20 (0.15-0.30) #
Combined RA with Method 2.2	3,253	17.7 (16.4-19.1)	0.20 (0.14-0.27) #
Combined RA with Method 2.3	3,253	17.6 (16.3-18.9)	0.19 (0.14-0.26)#
Combined RA with Method 2.4	**3,253**	**17.5 (16.2-18.8)**	**See Table 3**

Abbreviations: CPR – cardiopulmonary resuscitation, ROSC – return of spontaneous circulation, ED – Emergency Department, OR – Odds Ratio, CI – Confidence Interval. ***- Covariates:** age, male, public location, vfvt presenting rhythm, ems witness status, ROC sites 1-10.

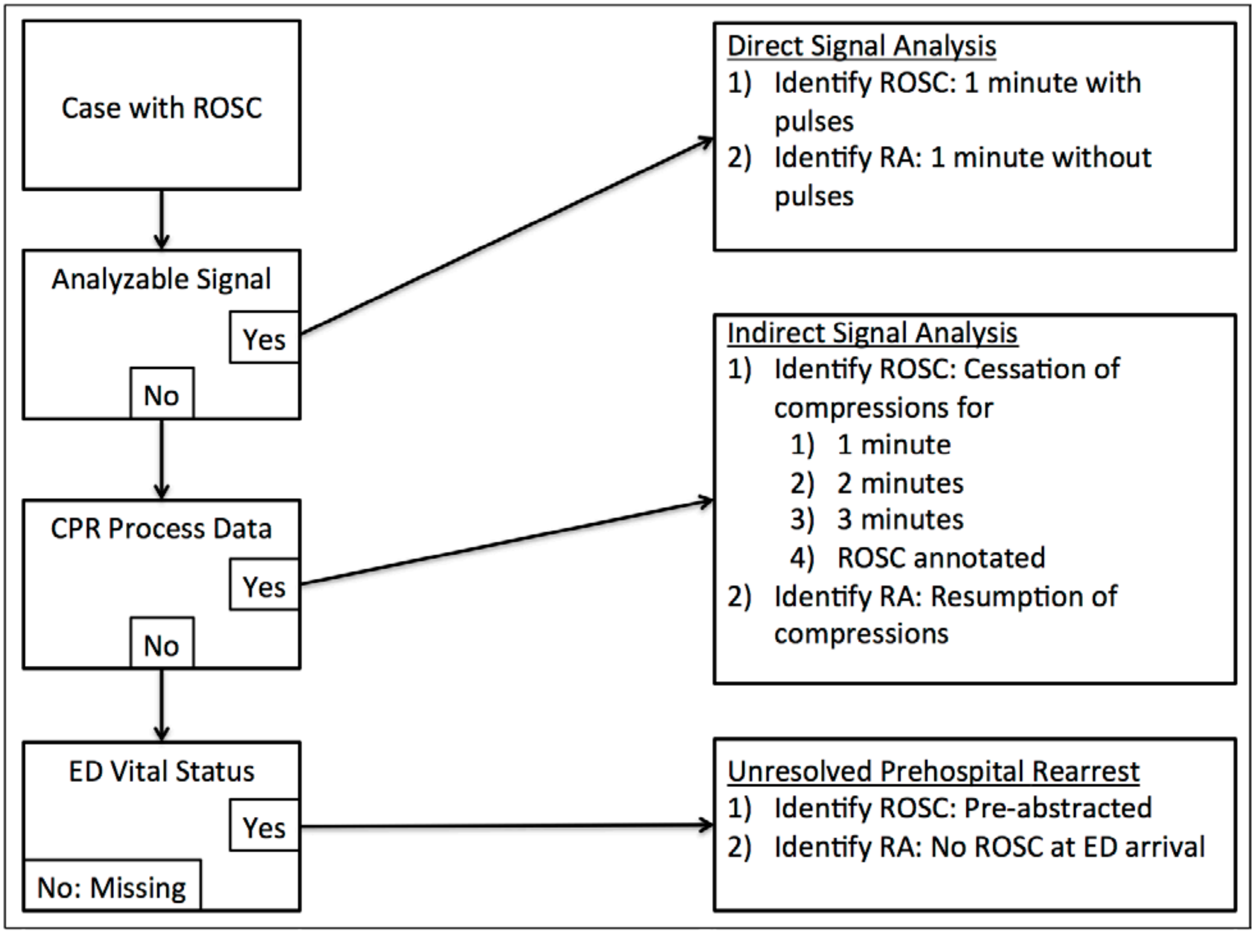
 # - Statistically significant at 0.05 level

Table 14A. Multiple Logistic Regression Results

Predictor	OR	95%CI	p
Rearrest (Method 2.4)	0.19	0.14-0.26	<0.001
Age, y	0.98	0.97-0.98	<0.001
Male	1.16	0.94-1.42	0.17
Public Location	1.99	1.61-2.46	<0.001
VFVT Presenting Rhythm	5.30	4.36-6.45	<0.001
EMS Witnessed	2.98	2.27-3.90	<0.001
Site A	0.98	0.69-1.41	0.93
Site B	1.33	0.98-1.80	0.07
Site C	0.69	0.49-0.97	0.03
Site D	0.46	0.12-1.69	0.24
Site E	1.77	1.12-2.78	0.01
Site F	0.74	0.55-1.01	0.06
Site G	1.02	0.61-1.72	0.93
Site H	1.68	0.97-2.91	0.07
Site I	0.80	0.41-1.57	0.52
Site J	ref	ref	ref

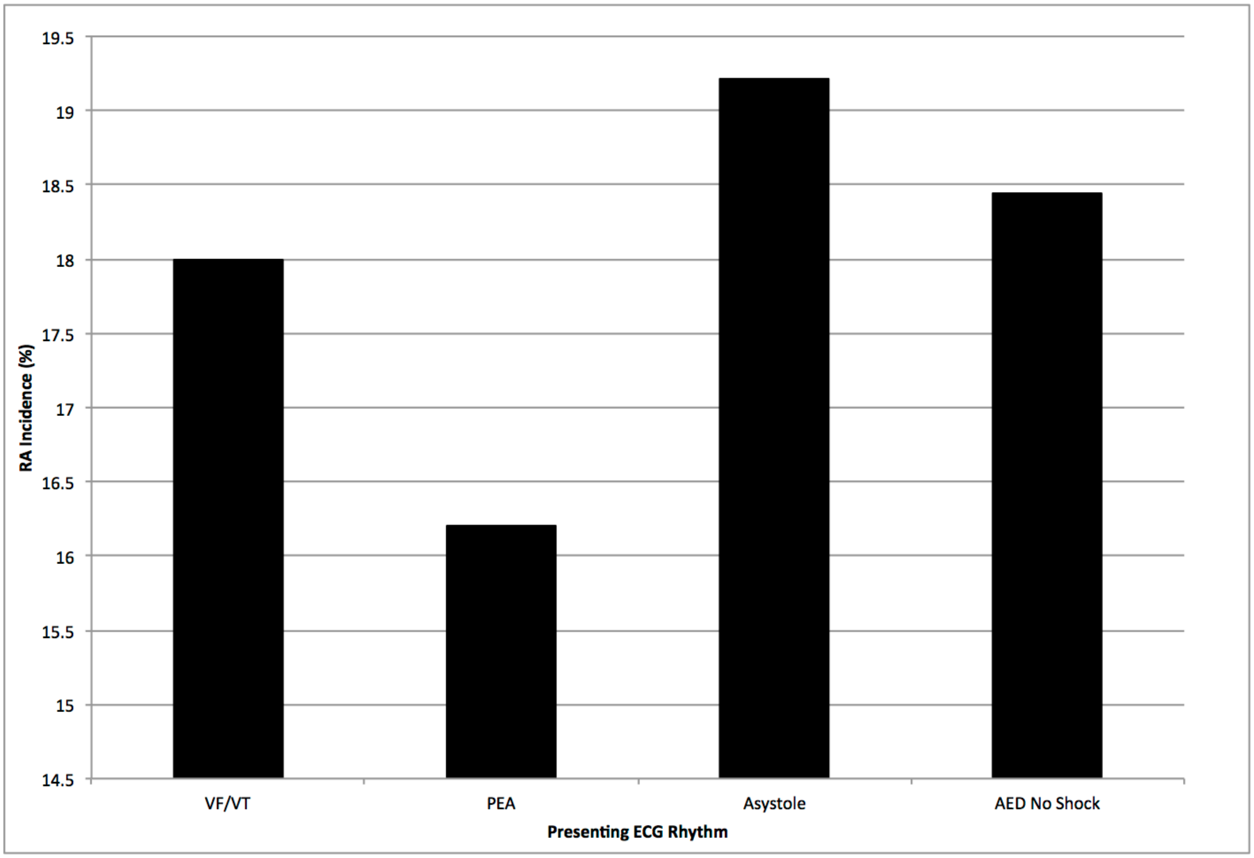
Abbreviations: VFVT – Ventricular Fibrillation / Ventricular Tachycardia, EMS – Emergency Medical Services, OR – Odds Ratio, CI – Confidence Interval

FIGURES



Abbreviations: ROSC – Return of Spontaneous Circulation, RA – Rearrest, ED – Emergency Department, CPR – Cardiopulmonary Resuscitation

Figure 8A. Rearrest Ascertainment Methodology



Abbreviations: VFVT – Ventricular Fibrillation / Ventricular Tachycardia, PEA – Pulseless Electrical Activity, AED – Automated External Defibrillator, RA – Rearrest

Figure 9A. Rearrest Incidence by Presenting ECG Rhythm

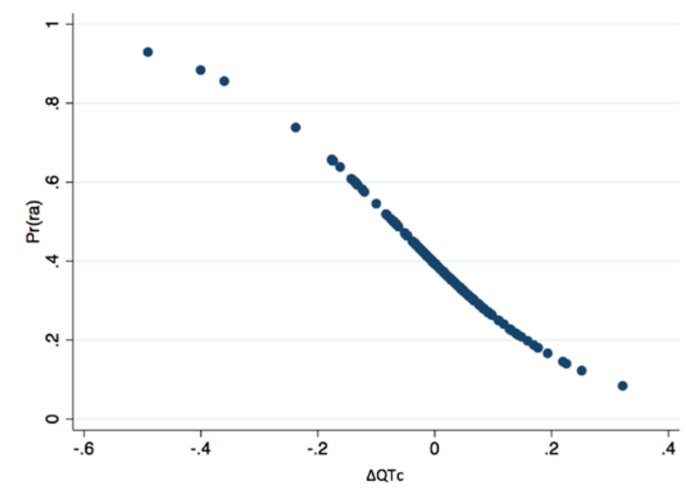
APPENDIX B: CASE CHARACTERISTICS FOR PATIENTS WITHOUT ANALYZABLE ECG

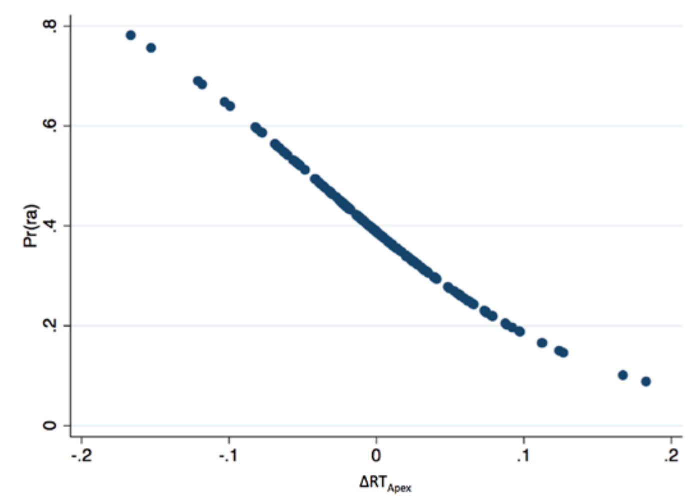
Characteristic	Overall	ECG (-)	ECG (+)	p
Age, y	63.8 (17.0)	63.9 (16.9)	61.9 (17.5)	0.100
Male, %	63.6 (61.9 – 65.3)	63.6 (61.9 – 65.3)	63.9 (57.4 – 70.5)	0.914
Median Income, $US	52857 (21344)	53109 (21566)	48595 (17132)	0.010
Public Location %	21.9 (20.5 – 23.3)	21.7 (20.2 – 23.1)	25.5 (19.6 – 31.4)	0.199
Bystander Witnessed %	62.8 (61.0 – 64.7)	62.6 (60.8 – 64.5)	65.6 (58.6 – 72.5)	0.435
EMS Witnessed %	12.6 (11.5 – 13.8)	12.7 (11.5 – 13.9)	11.5 (7.2 – 15.9)	0.630
First ECG Rhythm VF/VT %	44.3 (42.5 – 46.0)	43.7 (41.9 – 45.5)	52.4 (45.6 – 59.2)	0.015
Non-Cardiac Cause, %	8.1 (7.2 – 9.0)	8.3 (7.3 – 9.3)	4.8 (1.9 – 7.7)	0.072
Time to EMS CPR, minutes	9.6 (7.8)	9.6 (7.7)	10.3 (8.6)	0.177
Time to ROSC, minutes	24.2 (12.6)	24.2 (12.7)	24.7 (12.1)	0.559

Abbreviations: CPR – Cardiopulmonary Resuscitation; ECG – Electrocardiogram; EMS – Emergency Medical Services; ROSC – Return of Spontaneous Circulation; RA – Rearrest; VF/VT – Ventricular Fibrillation / Ventricular Tachycardia;

APPENDIX C: ON CHOOSING A PRACTICAL CUTPOINT FOR PREDICTING REARREST FROM QT-DERIVED METRICS

Shown below are univariate predicted probabilities of RA modeled on 1) ΔQTc and 2) ΔRT_{Apex}. Implications for choice of an optimal cutoff point in a multivariable model are unclear.





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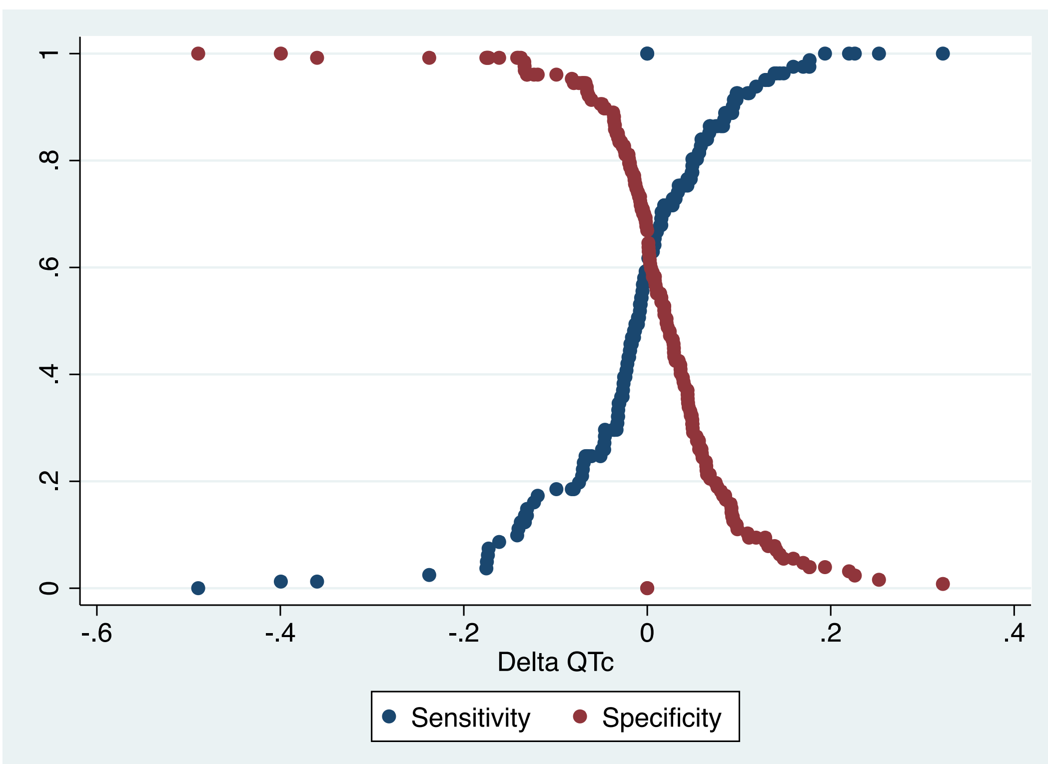
The following plot shows the relationship between sensitivity, specificity and ΔQTc in a univariate logistic regression model with outcome rearrest. For prediction of rearrest, sensitivity must be maximized at the expense of specificity, since the consequences of vigilance corresponding to suspicion of an impending rearrest are less serious than not anticipating rearrest.

The following plot shows the sensitivity/specificity tradeoff with increasing ΔQTc. Selection of a cutoff of ΔQTc = 0.13 results in a sensitivity of 95.1%, a specificity of 9.4%, and a positive predictive value of 39.7%.



Similarly, selection of a cutoff of ΔRT_{Apex} = 0.08 results in a sensitivity of 95.0%, a specificity of 9.4%, and a positive predictive value of 39.8%.

APPENDIX D: PRE-/POST-ROSC RHYTHM

The following results were excluded at thesis advisor's request for exceeding scope of proposed work. Future work will attempt to elucidate its validity and significance.

2 X 2 Table of Survivors Versus Rhythm Transitions (First Rearrest)

Symbols:

- **- - Asystole/PEA to Asystole/PEA**
- **-+ Asystole/PEA to VF/VT**
- **+- VF/VT to Asystole/PEA**
- **++ VF/VT to VF/VT**

	Dead	Surv.	Total
Transition (below)			
-- *,count*	11	0	11
Row %	100	0	100
-+ *,count*	17	2	19
Row %	89.47	10.53	100
+- *,count*	7	0	7
Row %	100	0	100
++ *,count*	17	14	31
Row %	54.84	45.16	100
Total	52	16	68
	76.47	23.53	100

Note: As shown here, transitioning to Asystole/PEA at first rearrest is deterministic for non-survival.
Abbreviation: PEA – pulseless electrical activity; Surv. – survival to hospital discharge.

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