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Improving survival in out of hospital cardiac arrest a prospective synthesis of best practice

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Thesis

IMPROVING SURVIVAL IN OUT OF HOSPITAL CARDIAC ARREST
A PROSPECTIVE SYNTHESIS OF BEST PRACTICE

by

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ABSTRACT

Cardiac arrest is the leading cause of death in the United States. By reviewing and analyzing the successes and failures of resuscitation efforts, it has been possible to identify critical components which have come to be known as the “Chain of Survival:” Early Recognition, Early CPR, Early Defibrillation, Early ALS, and Early Post Resuscitative Care. A failure in any one of the five links will result in a failed resuscitation.

Early Recognition is the beginning of the resuscitation effort and includes a number of related components. Witnessed cardiac arrests, those that are seen or heard to occur, have a significantly higher chance of survival than those which are unwitnessed. Properly identifying agonal gasps: irregular, forceful, reflexive breaths which can occur during cardiac arrest, is key to recognition of arrest and activation of the emergency response system. Emergency dispatchers trained to recognize cardiac arrest, as well as to initiate Early CPR via telephonic instruction, have been identified as key personnel in the resuscitation effort. Once professional rescuers have been dispatched, response delays due to distance and traffic can be costly. The use of new technologies like GPS and traffic signal preemption (as well as the use of Police, Fire and EMS in conjunction) has
been shown to make it possible to get qualified persons to the scene of a cardiac arrest more safely and more quickly.

Once on scene, early, high quality CPR has been shown to dramatically improve survival. After just 8 minutes without assistance, a victim of cardiac arrest has a near zero percent chance of survival. CPR of high quality has been shown to help maintain survivability until more definitive care can be obtained. Early Defibrillation is another key component to survival in many cardiac arrests. While CPR can sustain organ function briefly, cardiac arrest is rarely reversed without defibrillation. Increasingly widespread prevalence of public automated external defibrillators (AEDs) has made Early Defibrillation easier. Furthermore, increased use of AEDs by lay and professional rescuers has called into question the value of more traditional, higher risk interventions like intubation and medication administration. Early ALS interventions have been a staple of resuscitation for decades, but there is little data to support the use of these interventions during cardiac arrest. Early Post-Resuscitative Care, however, has been shown to be an area where invasive ALS interventions can and do make a difference in improved survival.

By looking at the body of research for links in the Chain of Survival, opportunities for improvement of resuscitation were identified. Persons who spend significant time around an individual at high risk for heart disease should be educated on possible precipitating symptoms of a myocardial infarct or other early signs of potential cardiac arrest. Persons likely to encounter a cardiac arrest should likewise be trained not only in how to recognize cardiac arrest (through the combination of unresponsiveness and
abnormal breathing) but also to initiate basic care via compressions-only CPR.

Emergency dispatchers should be increasingly trained to recognize cardiac arrest, as well how to effectively provide dispatcher assisted CPR. The focus of these efforts should be high quality CPR and the early deployment of defibrillation. The use of AEDs by bystanders should be encouraged whenever possible. The emphasis on CPR and use of an AED should be paramount, with invasive ALS interventions eschewed for the simpler and more effective therapies. Once ROSC has been obtained, the use of ALS interventions in unstable patients has been shown not only to prevent death due to transient hemodynamic instability, but also to improve the likelihood of survival with little to no neurological deficit. By embracing the chain of survival, and identifying the critical areas in need of research and improvement, it is possible to provide recommendations that may lead to improved survival from cardiac arrest.
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<td>ACLS</td>
<td>Advanced Cardiac Life Support</td>
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<td>AED</td>
<td>Automated External Defibrillator</td>
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<td>American Heart Association</td>
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<td>Advanced Life Support</td>
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<td>Basic Life Support</td>
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<td>Blood Pressure</td>
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<td>BVM</td>
<td>Bag Valve Mask</td>
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<td>CARES</td>
<td>Cardiac Arrest Registry to Enhance Survival</td>
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<td>CAD</td>
<td>Coronary Artery Disease</td>
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<td>CCR</td>
<td>Cardiocerebral Resuscitation</td>
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<td>CO</td>
<td>Cardiac Output</td>
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<td>CPC</td>
<td>Cerebral Performance Category</td>
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<td>CPR</td>
<td>Cardiopulmonary Resuscitation</td>
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<td>CQI</td>
<td>Continuous Quality Improvement</td>
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<tr>
<td>DaCPR</td>
<td>Dispatcher-assisted CPR</td>
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<tr>
<td>DAG</td>
<td>Diacyl Glycerol</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>EMS</td>
<td>Emergency Medical Services</td>
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<td>ER</td>
<td>Emergency Room</td>
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<td>ERC</td>
<td>European Resuscitation Council</td>
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<td>E&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>End Tidal Carbon Dioxide</td>
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<tr>
<td>ETI</td>
<td>Endotracheal Intubation</td>
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<td>GPCR</td>
<td>G protein-coupled receptor</td>
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<td>ICD</td>
<td>Implantable Cardioverter Defibrillator</td>
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<td>ICU</td>
<td>Intensive Care Unit</td>
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<td>IP3</td>
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<td>ITD</td>
<td>Impedance Threshold Device</td>
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<td>Mean Arterial Pressure</td>
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<td>NRB</td>
<td>Non-rebreather Mask</td>
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<td>OOH</td>
<td>Out of Hospital</td>
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<td>OHCA</td>
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<td>Return of Spontaneous Circulation</td>
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<td>Sudden Cardiac Arrest</td>
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<td>SGA</td>
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<td>STEMI</td>
<td>ST Segment Elevation Myocardial Infarct</td>
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<tr>
<td>TH</td>
<td>Therapeutic Hypothermia</td>
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<td>TPR</td>
<td>Total Peripheral Resistance</td>
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<td>TSP</td>
<td>Traffic Signal Preemption</td>
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<td>Targeted Temperature Management</td>
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<td>VF</td>
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<tr>
<td>VT</td>
<td>Ventricular Tachycardia</td>
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INTRODUCTION

Lateat scintillula forsan
Perhaps a little spark may yet lie hid¹

Each year almost 1,000 cardiac arrests a day are assessed by Emergency Medical Services (EMS) in an out of hospital (OOH) setting.² Attempts at resuscitation have been recorded as early as the sixth century, when primitive intubation was performed on crippled animals, and has been treated scientifically since the founding of the Amsterdam Rescue Society in 1767.³,⁴ Modern Cardiopulmonary Resuscitation (CPR), however, has existed only since 1960 when Kouwenhoven, Guy and Knickerbocker first demonstrated “Closed-Chest Cardiac Massage.”⁵ This discovery changed the face of modern medicine and helped shape the path for modern EMS with the ability to return a victim from “clinical death,” the absence of pulses, before reaching true “biological death,” where gross organ damage makes resuscitation impossible.¹ Survival to discharge with good neurological outcome (henceforth referred to as survival) is the ultimate goal of all resuscitation efforts.

Pathophysiology of Cardiac Arrest

Understanding both the global and cellular-level effects of ischemia due to acute dysfunction of the myocardium is critical to the successful treatment of cardiac arrest. Research that deconstructs cardiac arrest into various phases has shown promise in identifying different resuscitation strategies based on the amount of time elapsed since the initial disruption in cardiac function. The so-called three phase model proposed by
Weisfeldt and Becker looks to address the factor of time as a means of improving outcomes for victims of Out of Hospital Cardiac Arrest (OHCA).  

Extensive research, initiated by Dr. Lance Becker, on the molecular effects of ischemia on cells of the myocardium has illustrated that not only necrosis, but also apoptosis, affect the size of infarct and overall cardiac and metabolic dysfunction post cardiac arrest. Hypoxia, nutrient deprivation, the effects of reactive oxygen species (ROS), and damage to DNA from a variety of sources have all been shown to trigger apoptotic proteins. Becker showed that in many cases cell lysis and death did not occur until the reperfusion of tissue and thus the reintroduction of molecular oxygen post-ischemia. This Ischemia/Reperfusion (I/R) Injury has become the leading avenue of research for the molecular analysis of cardiac arrest.

The work of Dr. Becker initiated a dramatic paradigm shift in resuscitation science and practice. While prompt reperfusion leads to the reversal of the ischemic state and the restoration of ATP levels, it also contributes to the initiation of reperfusion injury. Research has shown that oxidative stress, membrane structure alteration, neutrophil-mediated inflammation, microvascular deficit, tissue edema, and energy depletion all contribute to I/R injury.

Regional Variation

The basic CPR premise of “push hard and fast in the center of the chest” remains, but there is significant variation in EMS training and standards of practice across the country. The Cardiac Arrest Registry to Enhance Survival (CARES, the largest registry
of US OHCA data) lists national OHCA survival for the US at around 10%. However, analysis of locations across the US and Canada by the Resuscitation Outcomes Consortium (ROC) has demonstrated variation between 3 and 16%, a five-fold difference, for survival rates of EMS-treated OHCA (See Appendix A - Tables 1 and 2). However, analysis of locations across the US and Canada by the Resuscitation Outcomes Consortium (ROC) has demonstrated variation between 3 and 16%, a five-fold difference, for survival rates of EMS-treated OHCA (See Appendix A - Tables 1 and 2). Seattle, Washington, for example, boasts a survival from ventricular fibrillation (VF) OHCA of almost 50% while Portland, Oregon, with similar population demographics, has a survival due to VF OHCA around 22%; less than half that of Seattle. Regional variations likely exist due to an uneven distribution of quality OHCA management, in both hospital and OOH settings but without mandatory data collection, and substantial databases for data collection, it is difficult to ascertain with any certainty. Part of the difficulty in assessing OHCA by region is the variability in how OHCA is defined. Establishing databases like the CARES and ROC reduces complications in data analysis and allows for a better understanding of the current state of resuscitation in the United States. Simply increasing survival from OHCA from the national average of approximately 10%, to the reported median of 12%, would save some 7,000 lives annually.

**Chain of Survival**

Though resuscitation after cardiac arrest has been attempted for many years, there has been minimal improvement in overall survival of victims of cardiac arrest in the last thirty years. The fundamental principles of resuscitation after cardiac arrest are referred to as the “links in the Chain of Survival”, a term coined in 1991 by Cummins et al.
These steps are the essential components required to successfully resuscitate any OHCA. While updated in 2010 by Rea et al. (See Appendix B - Figure 1) the essence remains. The Chain of Survival consists of: Early Recognition, Early CPR, Early Defibrillation, Early Advanced Life Support (ALS) Care, and Early Post-Resuscitative Care. These steps correlate well to new data which identifies five key factors for survival in OHCA: 1) Bystander witnessed Sudden Cardiac Arrest (SCA), 2) EMS witnessed SCA, 3) Bystander CPR, 4)VF/VT as presenting rhythm, and 5) Prehospital Return of Spontaneous Circulation (ROSC). While occurrence of many of these five steps seems related to chance, there are strategies which can be employed to improve the likelihood of each occurring by making improvements to the Chain of Survival. Successful execution of the Chain of Survival increases the likelihood of survival to definitive care in the ER or Intensive Care Unit (ICU), maximizing the chance of overall survival.

Early Recognition

With improvements in dispatching and cellular/mobile device technology, as well as centralized systems for the integration and triage of “911” calls, recognition has improved dramatically in recent years. A greater portion than ever of the general population are able to recognize the signs of cardiac arrest and, together with improved technology, recognition has improved. Though recognition of SCA has improved in recent years, continued efforts to increase recognition of SCA are important in reducing “time down:” the time between SCA and implementation of resuscitation. Training in early recognition of signs and symptoms leading up to SCA, as well as training in CPR
by bystanders and 911 dispatchers in Dispatcher-assisted CPR (DaCPR) can improve the percentage of SCA which are identified and which receive early intervention.\textsuperscript{16, 21}

\textit{Early CPR and Defibrillation}

Data as far back as 1980 has shown that Early CPR improves survival rate by up to 11.5 times.\textsuperscript{16} Improving the availability of CPR in witnessed and unwitnessed SCA can have a dramatic impact on survival rate.\textsuperscript{20} Likewise, improving the overall quality and efficiency of CPR is also essential to improving OHCA outcomes.\textsuperscript{7, 22, 23} Public access defibrillation (PAD), the publicization and wider use of publicly available automatic external defibrillators (AEDs), can double survival for victims of OHCA in a public location.\textsuperscript{24, 25} The increased prevalence of AED, and an increased willingness of bystanders to utilize them, holds promise for improvement of public area SCA.\textsuperscript{6, 26}

\textit{Early ALS}

ALS is perhaps the most contentious of the links in the chain of survival. Varying greatly by region, there is currently data both supporting\textsuperscript{27} and discouraging\textsuperscript{28} the use of ALS in OHCA. As described by the American Heart Association (AHA), Advanced Cardiac Life Support (ACLS) incorporates ALS, intravenous (IV) access, and medication administration, as well as placement of advanced airways [endotracheal tubes (ETI) and supraglottic airways (SGA)] and manual defibrillation (which will not be discussed herein).\textsuperscript{29} This paper will assess the state of current literature regarding the use of ALS care for the treatment of OHCA.\textsuperscript{27, 30, 31}
**Early Post-Resuscitative Care**

Treatment of “post-arrest syndrome” which includes: 1) Post-arrest brain dysfunction, 2) Post-arrest myocardial dysfunction, 3) Systemic ischemia/reperfusion response, and 4) Persistent precipitating pathology, is coming to be more and more appreciated as a vital link in the Chain of Survival and varies significantly between regions. Maintaining normal oxygenation and ventilation, as well as measures of cardiovascular function [blood pressure (BP), mean arterial pressure (MAP), and cardiac output (CO)], is associated with superior survivability and neurological function. Recent studies have lent growing support for the use of therapeutically induced hypothermia, hemofiltration, and extracorporeal membrane oxygenation (ECMO) to remove metabolic waste products post-arrest, in improving SCA outcomes. While there are numerous studies currently examining options for post-resuscitative care, a limited number which are feasible in an OOH setting will subsequently be explored.
REVIEW AND ANALYSIS OF PUBLISHED STUDIES

Utstein style

A uniform understanding of terms is essential for the proper assessment and continued improvement of resuscitation. Initially proposed in 1990 at the European Resuscitation Council (ERC) meeting at the Utstein Abbey in Norway, the Utstein guidelines provided recommendations agreed upon by the AHA, ERC, the Heart and Stroke Foundation of Canada and the Australian Resuscitation Council [together known as the International Liaison Committee on Resuscitation (ILCOR)] for the classification and reporting of OHCA. The original Utstein guidelines provided a number of definitions of potentially variable terms as well as a template which outlined essential data points to be reported for all OHCA. The initial guidelines focused on witnessed VF arrests, believing that isolating a single form of OHCA would aid in providing a point of comparison between agencies, organizations and nations.

There have since been major updates, notably the 2002 meeting of the ILCOR where definitions were updated, and the series of meetings between 2012 and 2014 summarized in Perkins et al.’s 2015 update of the Utstein template (See Appendix B - Figure 2). The 2002 updated definitions for the 21st century reclassified data as “core:” absolute minimum for continual quality improvement (CQI) and “supplementary:” required for resuscitation research, attempting to simplify a somewhat unwieldy process for a wider audience, and for data submission from non-researchers. By creating a simple template, the goal of reporting data from the chaotic and stressful scene of OOH resuscitation was simplified for post-hoc analysis. This update also
changed the reporting of OHCA to include arrest of all presumed cardiac etiologies, not just VF, thus allowing for the isolation of VF arrests but not limiting data to those cases alone.\textsuperscript{36}

The most recent Utstein update, published in 2015, had a dual purpose.\textsuperscript{37} First, elements of an OHCA call were organized into five categories: System, Dispatch, Patient, Process, and Outcome. Together these five categories encompass the various elements needed for the assessment of OHCA data.\textsuperscript{37} Second, and perhaps more significantly, the Utstein template was simplified to aid those not necessarily involved explicitly in resuscitation science research.\textsuperscript{37} This update has provided a framework for the universal comprehension and interpretation of OHCA benefiting all involved in resuscitation research.\textsuperscript{37}

As a whole, the Utstein guidelines allow for the comparison and analysis of OHCA. The guidelines focus on “witnessed cardiac arrest due to presumed underlying heart disease, with the initial rhythm of ventricular fibrillation.”\textsuperscript{1} By using these criteria to report so-called “save rates,” legitimate comparisons between agencies are made possible. At this time, however, the guidelines remain imperfect with definitions such as “survival” (to admission?, to discharge?, at 30 days?, at 90 days?) poorly defined.\textsuperscript{36}

\textbf{Pathophysiology of Cardiac Arrest}

As defined by the Utstein guidelines, cardiac arrest is “the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.”\textsuperscript{36}

Understanding the pathophysiology of cardiac arrest, and of the dysfunction immediately
post-arrest, allows for a better understanding of the methodology behind strategies of resuscitation and gives insight into how various interventions might be utilized for the best possible outcomes.

First proposed in 2002 by Weisfeldt and Becker, the “three phase model of cardiac arrest” was created in an attempt to better understand how time after onset of VF/VT cardiac arrest altered the physiology of the body (See Appendix A - Table 3 for Summary). This theory posits that there are three distinct phases of cardiac arrest, wherein different interventions may be ideal for successful resuscitation. In the electrical phase, the heart has recently ceased pumping and is thus in a sort of pause state. Defibrillation in this phase is believed to function like a reset, converting from a non-perfusing to a perfusing rhythm and allowing for the resumption of normal, or at least life-sustaining, cardiac activity.

The electrical phase theory is supported by animal data, where studies have shown that approximately 3 minutes post arrest is the threshold for high probability of successful defibrillation. Data from Implantable cardioverter defibrillators (ICD) further supports this threshold. ICDs shock between 15-20 seconds after VF and are almost 100% effective at converting dysrhythmia. Furthermore, witnessed arrests where security personnel or police are able to defibrillate (administer a shock) early have much better outcomes, with some studies suggesting convertibility with immediate defibrillation at almost 100%. This is explained in part by the changing cardiac activity observed on an electrocardiogram (ECG). Initial ECGs of, in particular VF, SCA show a coarse waveform (See Appendix B - Figure 3). Later ECGs show progressively finer
waveforms until there is ultimately asystole, or “flatline” (See Appendix B - Figure 3). Early CPR can sustain coarser waveforms, which have better likelihood of defibrillation to a perfusing rhythm.\textsuperscript{1, 7, 41} Data has shown that victims of OHCA that occur in casinos, where there is a preponderance of trained security and available AEDs, have a significantly higher chance of survival as compared to nearly any other location.\textsuperscript{20} Early defibrillation alone with no other significant intervention has shown survival rates approaching 50%.\textsuperscript{24}

Though equally well documented, the circulatory phase is less well understood. It is believed to be the result of a privation of nutrients to starved tissue and the need to remove toxins.\textsuperscript{6} Cherry et al. report that “modest delivery of O\textsubscript{2} and metabolic fuels to the myocardium… may support enough myocardial ATP production to sustain ion transport and repolarize cardiomyocytes, enabling defibrillatory countershocks to restore spontaneous electrical rhythm.”\textsuperscript{38} Various studies have shown that human data supports this model.\textsuperscript{6, 42} A study conducted in Oslo, Norway demonstrated an improvement in survival from 4 to 22\% when 3 minutes of CPR was performed prior to defibrillation, when EMS arrived greater than 5 minutes after arrest.\textsuperscript{6} Another study in the US showed an increase in survival of 24 to 30\% in patients who received 90 seconds of CPR prior to attempted defibrillation.\textsuperscript{6} Because of variability in EMS response times, an understanding of the circulatory phase of cardiac arrest appears to be a critical area for future research.

The metabolic phase does not currently provide a promising landscape for potential resuscitation. The metabolic phase occurs when global ischemia triggers a sepsis-like inflammatory state.\textsuperscript{6} Once this phase has begun, there is a decidedly lower
chance of biological survival and almost no hope for good neurological outcome.\textsuperscript{6, 38, 42} A large, multiyear retrospective study in Washington state showed that at approximately 11 minutes after SCA, there is a marked decrease in the efficacy of bystander CPR, seemingly corresponding to the purported “metabolic phase.”\textsuperscript{6, 42} This is further supported by the lack of reported survival for any patient where it took longer than 15 minutes to initiate CPR.\textsuperscript{42}

While growing in acceptance, the extreme difficulty in identifying the proposed stages currently limits the utility of the application of the three phase model in an EMS or hospital setting. There is also data suggesting various adjustments in the timing of phases extending the electrical phase up to 5 minutes and the circulatory phase up to 15 minutes.\textsuperscript{42} Despite this variability in definitions and the current inability to detect phases, ECG waveform morphology has shown some sensitivity as an indicator of “time down” but is as yet imperfect.\textsuperscript{6} The three phase model of VF/VT arrest remains promising and is the subject of much current research.\textsuperscript{6, 38}

Equally critical for an understanding of cardiac arrest survival is the comprehension of the physiology behind post-arrest dysfunction. The phenomenon of so-called cardiac “stunning,” transient (24 to 48 hours) myocardial dysfunction in the aftermath of SCA (See Appendix B - Figure 4), has been observed for decades and is partially the result of myocardial ischemia (the predominant cause of VF/VT arrest).\textsuperscript{38, 44} More recently, the observations of Dr. Lance Becker at the University of Pennsylvania have revolutionized the understanding of post cardiac arrest morbidity.\textsuperscript{45} Becker observed, initially in chick cardiomyocytes, that cells appeared to die only after oxygen
was reintroduced.\textsuperscript{45} Loor et al., using cell cultures, found that mitochondria exposed to ischemia, but that did not undergo reperfusion, demonstrated blebbing and rounding, but no lysis.\textsuperscript{8} Based on these observations, Dr. Becker proposed the idea of I/R injury, a concept that has quickly become a foundational component of our understanding of resuscitation science.\textsuperscript{45} Reperfusion injury after myocardial ischemia can cause arrhythmias, myocardial stunning, increased infarct size, and other forms of damage.\textsuperscript{46} In fact, with regard to myocardial stunning, the most severe hemodynamic instability is often delayed for four to seven hours, corresponding to peak oxidative stress.\textsuperscript{43, 44}

Cardiac arrest induces global ischemia, particularly in the brain and heart, which require a constant supply of glucose. Interrupted blood supply prevents adequate nutrient delivery and proper removal of metabolic waste products.\textsuperscript{46, 47} The lack of oxygen supply to tissue induces a shift to anaerobic metabolism. This change in metabolism leads to a shift in ion channel function which, through the inhibition of ATPases, results in increases in intracellular Na\textsuperscript{+} and Ca\textsuperscript{2+} which adversely effects cell function.\textsuperscript{46} Calcium overload can trigger proteases, potentially causing permanent structural damage, and lead to necrosis.\textsuperscript{8} For years, the definitive treatment for ischemia has been prompt reperfusion.\textsuperscript{4, 7, 48} By reperfusing tissue via defibrillation, and coronary revascularization, molecular oxygen is restored, allowing for cellular respiration to occur.

After oxygenation is restored, there is a phenomenon, based on the previously mentioned work of Dr. Becker, called Ischemia/ Reperfusion (I/R) injury. It is proposed that ROS are responsible for I/R.\textsuperscript{8, 9, 45-48} When oxygen is restored to ischemic tissue, myocardial mitochondria produce a surge of ROS.\textsuperscript{49} These ROS cause lipid peroxidation
as well as alteration of proteins and potentially DNA, a process known as oxidative stress.\textsuperscript{47} Markers of oxidative stress have been shown to correlate to post-arrest myocardial dysfunction.\textsuperscript{43} When oxidative stress biomarkers returned to baseline approximately 72 hours post-reperfusion, measures of myocardial function likewise were shown to improve.\textsuperscript{47}

Lipid and protein alteration can lead to small molecule influx, including $\text{Ca}^{2+}$ and $\text{Na}^{+}$, via the sarcolemmal and mitochondrial membranes, leading to lysis as water follows the small molecules.\textsuperscript{10, 46, 49} As a whole, the I/R process has a dual peak for $\text{Ca}^{2+}$ concentration, initially occurring between fifteen and sixty minutes after onset of ischemia and then again approximately thirty minutes after reperfusion.\textsuperscript{9, 10} It is proposed that this increase in membrane permeability contributes to cell death by causes irreversible changes which lead to apoptosis.\textsuperscript{8}

Because of the importance of mitochondria in the generation of ROS, detailed studies of mitochondrial response to I/R injury have contributed greatly to our understanding of I/R injury.\textsuperscript{8, 47} In a cell culture model of cardiac arrest, reperfusion induced cytochrome c release and, while this was initially believed to be an integral part of cell death, a model organism lacking cytochrome c was shown to still experience cell death.\textsuperscript{8} Studies by Kalogeris et al. have further complicated our understanding of ROS in I/R injury.\textsuperscript{47} These studies have shown that while ROS contribute to apoptosis and cell damage, as previously discussed, ROS also enhance cell repair and angiogenesis.\textsuperscript{46, 47, 49} Part of this beneficial role for ROS has been associated with ischemic pre-conditioning.\textsuperscript{7, 8} Patients with previous history of angina, and thus ischemia, have shown less chest pain,
less ST segment modulation on ECG, and in some cases smaller infarct size. This suggests that cells that are “used to” or “preconditioned” for ischemia fare better. While as yet poorly understood, it is believed that type, amount, and intracellular location of ROS could contribute to the varied effects observed. In healthy tissue, ROS are heavily regulated signaling molecules and structural modifiers of lipids and proteins. Because of this tight control, it is reasonable to assume that even a small alteration in type, amount, and location of ROS could lead to a significant alteration of cellular behavior.

Beyond its immediate intracellular role, oxidative stress also leads to an inflammatory response. Neutrophils are recruited via the inflammatory response, leading to further tissue damage. Neutrophil activation in the inflammatory post-ischemic state leads to increased vascular permeability, resulting in tissue edema as fluid leaks through the more permeable endothelium. This edema can occur in the pulmonary endothelium and lead to a reduction in gas exchange. Neutrophil-induced activation of the complement system has been shown to result in cell damage as well, with cell lysis perpetuating an autoimmune response. Neutrophils can also induce the “No-reflow Phenomenon” by narrowing vasculature and then physically occluding microcirculation even after blood flow has been restored to larger vessels. There is also evidence that myocardial necrosis can release cytokines which trigger the complement system. Inhibition of complement has been shown to reduce the size of infarct in animal studies.

What can be done with this knowledge of I/R injury to improve patient outcomes? Perhaps most critical is acting on the understanding of oxyhemoglobin concentrations. Hemoglobin oxygen saturation of between 94 and 98% has been shown to have similar
perfusion of tissue, with less reactive oxygen and nitrogen species, as compared to a saturation of 100%. There is an issue with intraarrest measurement of hemoglobin oxygen saturation, however, due to inaccuracy of peripheral transducers during arrest. The growing availability and post-ROSC accuracy of oxygen saturation transducers in EMS means that it is reasonable to have an expectation of titrated oxygen therapy during post-resuscitation care. This represents a simple and immediately impactful modification in treatment to improve the damage caused by I/R in the prehospital setting.

Other therapies, in the laboratory and in hospital settings, have also shown promise in the management of I/R injury. Post conditioning, brief periods of ischemia with alternating periods of reperfusion, has shown cardioprotective effects. While promising, there are limited circumstances where this appears to offer benefit and there is nothing that can be currently done in the prehospital setting to achieve this. Similarly, rat models have shown that pretreatment with antioxidants or overexpression of antioxidant enzymes can reduce I/R injury. These antioxidant therapies are as yet poorly understood and are not yet feasible in an OOH setting.

Though as yet primarily an intellectual exercise, understanding the macro effects of cardiac arrest, as shown by the three phase model described by Weisfeldt, and the molecular effects of I/R reperfusion injury, elucidated by Becker shows promise in identifying future treatments and avenues of study.
Early Recognition

Early recognition of SCA is critical to a positive outcome. For each minute that defibrillation is delayed, it has been suggested that the chance of survival decreases between 7 and 10%. Strategies to improve early recognition are, however fraught with limitations. The largest obstacle to early recognition, and thus early care, is witnessing the SCA. Between 25 and 37% of all OHCA are witnessed (seen or heard to occur). Witnessed SCA has a survival rate of approximately 33%, compared to a less than 10% survival for overall OHCA. In a hospital setting, patients at high risk for arrhythmia or dysrhythmia enjoy the benefit of constant monitoring via ECG but this is currently impractical in an at home setting.

Some studies have shown that up to 75% of cardiac arrest victims exhibited some potentially cardiac symptomology beforehand. These include the signs of a myocardial infarct (MI) such as chest, jaw, arm or back pain as well as tightness in the chest, shortness of breath, unexplained indigestion, and dizziness (as well as many other signs and symptoms). Identification of these symptoms can lead to prompt recognition of MI or arrhythmias and timely consultation of professional medical help via EMS and/or the ER. Early recognition of chest pain in particular can be essential for early identification of ST elevated MI (STEMI), which requires urgent coronary angiography and transport to an appropriately equipped facility. Early recognition also facilitates preventative care. A healthy population has an OHCA rate of 1/3,000 per year. Persons with known ischemic heart disease have a rate of 5/100 or 5% per year and patients with congestive heart failure have a rate of between 8 and 12% per year. “Aggressive
preventative care”, the use of statins for hypercholesterolemia and anti-hypertensive medications have reduced the incidence of cardiac arrest and heart disease by 59% and 49% respectively since the 1950’s.\(^1\)

There can also be significant confusion among lay rescuers, and even professional first responders, regarding whether cardiac arrest has occurred. Agonal gasps or respirations can occur in up to 40% of cardiac arrests.\(^{19, 20}\) Agonal gasping is described as a “primitive midbrain reflex” and is characterized by irregular, forceful bradypnea and is a clear marker of cardiac arrest.\(^{52}\) Both professional and lay rescuers often fail, however, to correctly identify agonal gasps as a sign of SCA.\(^{20, 52}\) This is an important concern because confusion regarding onset of cardiac arrest is associated with delays in 911 calls and thus delays in all subsequent steps in the chain of survival.\(^{20, 52}\)

The key interaction for improving Early Recognition, and subsequent Early CPR and Early Defibrillation, is that between 911 Dispatchers and the bystander who calls.\(^7, 57\) A 911 dispatcher must assume any call is a SCA until it is confirmed otherwise.\(^{19}\) First utilized in King County, WA in 1983, Dispatcher-assisted CPR (DaCPR) has been shown to increase the likelihood of a bystander performing CPR, trained or untrained, by 50% and is associated with a 50% increase in survival of VF/VT arrest.\(^1, 7, 57\) Two simple questions have been identified to determine the presence of cardiac arrest: (1) “Is the victim responsive or conscious?” and (2) “Is the victim breathing normally?”\(^{52}\) Negative responses to both questions triggers the OHCA algorithm (See Appendix B - Figure 5), with EMS and first responders dispatched immediately while DaCPR instructions are given.\(^1, 20, 57\) The importance of “breathing normally” has been expressed above and
teaching 911 dispatchers to identify bystander description of agonal respirations has been shown not only to increase cardiac arrest recognition by 911 dispatchers but also bystander CPR and overall survival from OHCA. A study using dispatchers in Washington state who had received 32 hours medical training, 6 of which were dedicated to recognition of OHCA and delivering CPR instructions via phone, showed successful identification of cardiac arrest 80% of the time. This is contrasted by a study using dispatchers not trained to recognize agonal gasps, in Arizona, which demonstrated a median time from initiation of 911 call to initiation of CPR of 4.2 minutes. This translated to a significant delay between time down and time of CPR. In general, DaCPR has been shown not only to improve the rate of bystander CPR performance, but also the survival rate with good neurological outcome.

Early arrival of EMS is the last area to be considered in the Early Recognition link. A response time of less than 8 minutes 90% of the time is the benchmark for many, if not most, EMS agencies. This response time of 8 minutes is based on a 1979 study of survival from non-traumatic OHCA. While this study laid the foundation underlying our understanding of response times, it is now outdated. The 7 to 10% per minute loss of viability mentioned earlier means that with an 8 minute response time added to the approximately 3 minutes it takes to arrive on scene and deliver a defibrillator shock, there is, a 0 to 24% chance of survival: consistent with the overall 10% survival observed in the US. While debated, the ideal time to defibrillation is believed to be somewhere around 5 to 6 minutes after onset of arrest.
The obvious solution for decreasing response times is to increase the number of ambulances. This, however, has been shown to be surprisingly ineffective, with an 80% increase in the total number of ambulances needed to reduce the response times by just one minute. A 2010 UK study showed that a 1 minute reduction in response times would cost approximately £54 million. Another solution is targeted posting of emergency units. Careful positioning of ambulances around areas with the highest likelihood for OHCA led to a reduction in average response time to OHCA from 10.1 to 7.1 minutes in Singapore. An approach that has been shown to be successful in a number of locations is “dual dispatching.” This process, which entails immediately dispatching other professional first responders like police and fire to all suspected OHCA has been shown to improve outcomes. King County, Washington, with a VF/VT survival rate approaching 60%, was one of the pioneers in the use of Firefighter EMTs to be dispatched as first responders to all ALS calls. In Stockholm, the use of Fire Department first responders retrained annually throughout the study was associated with, on average, a 1 minute reduction in response time; the same as an 80% increase in the number of ambulances, and with an increase in long-term survival from 2.4 to 6.5%. Rochester, MN has triple dispatching, with Fire, Police and EMS all sent to suspected OHCA. Rochester has an average time to defibrillation of 6 minutes and has the second highest rate of VF/VT survival in the United States. The EMS director for King County, Dr. Eisenberg describes first responder CPR and AED use as one of the easiest steps, “low-hanging fruit” in the improvement of OHCA.
Beyond changing how ambulances are dispatched, technologies have been shown to improve response times of the ambulances themselves. Traffic Signal Preemption (TSP) devices, a system which uses sound, light or radio signals from an emergency vehicle to change traffic signals, have been used for years in an attempt to reduce response times to trauma and cardiac arrest, as well as to reduce the incidence of emergency vehicle crashes at intersections.\textsuperscript{62} Used in the US since the 1960’s TSP has been shown to dramatically reduce delays caused by intersections.\textsuperscript{62} In 1978, using a primitive system, the city of Denver reported between 14 and 23\% reduction in response times.\textsuperscript{62} In the largest study of TSP in the US, Fairfax County, VA reported a time savings of 30 to 45 seconds per intersection.\textsuperscript{62} In that same study, Minneapolis, MN reported a dramatic reduction in emergency vehicle collisions at TSP-equipped intersections and Plano, TX reported a reduction in intersection crashes from 2.3/year to fewer than 1 collision/5 years as well as a 10-20\% reduction in response times.\textsuperscript{62} In Japan studies utilizing the so-called FAST device, a specific model of TSP, demonstrated a reported 54 second improvement, on average, in response time of Japanese ambulances.\textsuperscript{63} There was, unfortunately, no data provided about changes in the occurrence of accidents or vehicular complications.\textsuperscript{63} Based on improvements in response times for emergency vehicles using TSP devices, this technology could be expected to improve survival by 10\% based off models of VF/VT arrest.\textsuperscript{52, 62, 63}
Early CPR and Defibrillation

Once cardiac arrest is recognized, it is important to initiate CPR until an AED and/or professional responders arrive. Data shows that a victim of OHCA down just 8 minutes (response time goal since 1979) without CPR has a near 0% chance of survival.1, 52, 59 This alarming statistic reinforces that patients who receive bystander CPR have significantly better outcomes.20, 55, 56, 64 The improvements that dispatchers can make in bystander CPR has been known now for decades, but the importance of training that focuses on lay rescuers has been identified more recently as a key factor in improving the percentage of bystanders who initiate CPR.7, 20, 25, 52, 65, 66 In a study published in 2003, only two out of five patients presenting to the ER for chest pain came from a household with CPR training, although two thirds were willing to partake in CPR training when asked.7 Widespread focused training of bystanders, and training in high performance CPR for professional rescuers, can and does make a difference in survival from OHCA.7, 52, 66 Bystander CPR alone has been shown to double survival rates in Japan with survival jumping from 4 to 8% for patients who received bystander CPR of some kind.66

In general, the United States has grossly inadequate training of CPR amongst the general populace.67 An extensive study conducted by Anderson et al using data from the AHA, American Red Cross and the Health & Safety Institute, the body largely responsible for CPR training in the US, found an average CPR training rate of 2.39%/county.67 More frightening is that there were counties with a reported 0% training in CPR.67 There is some room for error due to the fact that the reported county is likely that in which the person was trained and not that in which they reside, as well as the fact that
this measures only those who obtained a certification in CPR and not more informal training. 57% of lower tertile counties were in the South and a disproportionate fraction of the lower tertile were in rural and/or low income populations. Black and Hispanic populations were also less likely to be trained in CPR regardless of socioeconomic status. The limited availability of EMS resources in these areas has been shown to have expectedly poor outcomes for critical illness. Special efforts must also be made to train individuals in rural, isolated areas, as well as in black and Hispanic communities, which tend to have increased rates of OHCA as compared to the population as a whole.

The value of CPR training is obvious, but with the ease of DaCPR the question of resource expenditure to educate large numbers of people about CPR has been an oft-raised question in recent years. Even with DaCPR, a higher percentage of laypersons trained in CPR was found to directly correlate to an improved frequency of bystander performance. Surveys of members of the public indicated that willingness to use an AED and confidence in CPR abilities increased substantially with training in CPR. Data of bystander CPR shows a dramatic increase in CPR performance for compressions-only CPR. This is logical when viewed in the light of survey data. The primary reasons reported for not undergoing training were cost, lack of information, and fear of risk to self in performing CPR. Risks of mouth to mouth resuscitation were found to be the critical factor for bystanders not performing CPR. Furthermore, compressions-only CPR has been shown to be at least as effective as conventional CPR for cardiac arrest of non-respiratory origin and can be taught in as little as sixty seconds. The increased
likelihood of bystander CPR with a compressions-only model led to an increase in survival from 3.7 to 9.8% in one study. DaCPR instructions that are “hands-only” have been shown to also increase bystander willingness to perform CPR. The combination of GPS and social media has also been shown to be a valuable tool in reducing time to early CPR. Self-enrolled lay rescuers targeted via mobile phone GPS and social media arrived on average after just 2 minutes and 20 seconds in urban Sweden, leading to a dramatic reduction in the time down for witnessed cardiac arrests. Similar studies in Holland were found to significantly reduce time to defibrillation for public area OHCA. Individuals were able to self-register online with their typical location during business hours. If a SCA occurred near an area where a registered user was typically located, a text message was sent which included the location of a nearby AED if applicable.

It is also critical to improve the quality of CPR performed by professional rescuers (See Appendix A - Table 4). Incomplete recoil of the chest leads to decreases in BP, MAP and perfusion to the heart and brain. In fact, a porcine model with incomplete thoracic recoil and positive pressure ventilations produced a cerebral perfusion pressure of near zero. In low flow situations, oxygen delivery is a function of flow rather than arterial O2 content. Because of this, the focus should be on compressions rather than ventilations with a bag valve mask (BVM). Metronomes and real time feedback devices such as waveform EiCO2 capnography have been shown to improve the portion of CPR within the ideal range. Despite recommendations by experts in the field, almost no published studies could be located assessing the value of
high fidelity CPR training. There was data for high fidelity ACLS, though every study encountered focused on nurses and the rest on residents or pharmacy students.\textsuperscript{81-86}

For witnessed arrests, immediate compressions without delay for ventilation has been shown to improve survival in most cases.\textsuperscript{56,57} Passive insufflation via non-rebreather mask (NRB) with an oropharyngeal airway (OPA), along with continuous compressions, has been shown to potentially improve outcomes for VF/VT arrest witnessed by healthcare providers.\textsuperscript{72,77} Other studies have looked at passive insufflation for unwitnessed or non-shockable arrests and the data has been largely in support of passive insufflation over standard CPR.\textsuperscript{75,77} However, these studies are underpowered to be definitive.\textsuperscript{75,77} Early and/or continuous compressions reduce the drop in perfusion caused by delays for ventilation and/or rescuer swaps.\textsuperscript{72,88,89} The duration of pauses affects the ability to build to a reasonable perfusing pressure during SCA.\textsuperscript{89} A delay of 10 seconds gives an 87\% chance to maintain or improve BP while a 15 second delay gives an approximately 67\% chance of maintaining or increasing BP.\textsuperscript{89} The longest single interruption in CPR has been shown to account for, on average, 30\% of total interruptions in CPR.\textsuperscript{88} When the longest pause is a non-shock interruption of any kind, survival has been shown to decrease by almost 50\%.\textsuperscript{88} Because of the fact that even ideal CPR represents less than 1/3 of normal coronary blood flow, and less than half of normal cerebral blood flow, maximizing BP during resuscitation, through ideal compressions and reduced interruptions remains the best way to improve survival.\textsuperscript{7,75,79,90}

Rib and sternal fractures were more frequent in OHCA than in hospital regardless of bystander CPR.\textsuperscript{91} Furthermore, increase in speed with which the ambulance travels has
been shown to increase rate and depth of compression.\textsuperscript{92, 93} Excessive depth increases chance of injury, and both excessive depth and rate decrease efficacy of pumping.\textsuperscript{77} Because of these facts, the manufacture of mechanical CPR devices has increased significantly. Two major forms of devices exist, a piston device placed on the chest, and a load-distributing band which is placed around the body. Though many studies have been made both prospectively and retrospectively, no data has been generated which shows an improvement in outcomes for patients who undergo mechanical CPR.\textsuperscript{94} Even during long resuscitations, when there is sufficient manpower, manual CPR is preferred.\textsuperscript{23, 57} Multivariate analysis, attempting to correct for extrication and complicated situations still demonstrated poorer outcomes with mechanical CPR devices.\textsuperscript{95} Because of this failure to show an improvement, and the potential harm of mechanical CPR devices, it is recommended that they should only be used where it would be impractical or unsafe to perform manual CPR.\textsuperscript{23, 57} Due to the possibility of an increased rate and depth, as well as risks to rescuers, it is not unreasonable to use mechanical CPR devices while an ambulance is in motion.\textsuperscript{87, 91, 92, 93, 94}

Recent research has identified the potential for adjuncts to manual CPR as more effective than fully mechanical CPR.\textsuperscript{94, 96} The active compression-decompression (ACD) device is a suction cup device similar to piston mechanical CPR devices. While standard CPR relies on the elasticity of the chest wall, the ACD device is designed to enhance the recoil action.\textsuperscript{96, 97} It was developed after porcine models demonstrated improved aortic BP, coronary and cerebral perfusion pressures, and increased cerebral $O_2$ delivery and uptake with the use of an ACD device.\textsuperscript{98} ACD CPR has been shown to have potentially
improved efficacy when used with an impedance threshold device (ITD). An ITD functions by limiting air into the lungs during decompression. This reduces intrathoracic pressure, thus increasing venous return and potentially reducing intracranial pressure. An ITD can be attached to a mask, ET tube, or SGA. However, ITD with traditional CPR has not been shown to have any improvement in survival, perhaps due to a possible increase in acidosis. ACD-ITD CPR has been shown in several trials to increase survival although with the suggestion of an increased rate of pulmonary edema. In general, data for ACD-ITD CPR, while promising, is namely specific to VF and is currently underpowered to suggest a large scale shift in policy.

While CPR is essential to maintain organ function, defibrillation is what allows for survival after the majority of cardiac arrests. Survival is reduced by up to 10% per minute without defibrillation. Those patients who never received defibrillation experienced a rate of survival of less than 1%. Defibrillation can be achieved with a manual external defibrillator, usually a component of a cardiac monitor that allows for current to be selected, or an AED which performs calculations based on rhythm and resistance detected. Though commonly referred to as automatic, the majority of AEDs are in fact semi-automatic external defibrillators, requiring manual shocking via a pushed button. The rarity, however, of true AEDs eliminates the need for clear distinction in this discussion. Implantable Cardioverter Defibrillators (ICD) are another means of defibrillation. ICD data demonstrates that immediate defibrillation of a VF/VT arrest can be almost 100% effective.
When King County, Washington first trained EMTs in defibrillation, VF arrest survival went from 7 to 26%. With AEDs now mandatory on ambulances nationwide, focus has shifted to the further improve time to defibrillation, with use of an AED ideally occurring prior to EMS arrival. One study using ROC data demonstrated 38% of victims of OHCA who receive defibrillation prior to EMS arrival survive. This is in comparison to a study-specific total survival of 7% and 9% with bystander CPR alone. Early ROSC is key to survival with nearly ¾ of patients with good outcomes achieving ROSC prior to 9 minutes after SCA and nearly 90% of good outcomes with ROSC at 15 minutes after SCA. Overall, public use of an AED has been shown to nearly double the chance of survival. Some 20% of all OHCA will occur in a public place and public access to AEDs can make a significant difference in outcomes in public locations. The AHA and federal government both support plans for PAD in locations of high risk such as senior centers, gyms, etc.

*Early ALS*

Research into the efficacy of ALS treatments in cardiac arrest, and for the purposes of this analysis OHCA, looks at either ALS as a whole or the individual procedures and/or medications therein. The specific areas of research that most merit discussion are the value of medication administration in OHCA as well as the value of advanced airway placement during CPR.

The first main category of pharmacological agents used in ACLS is vasoactive compounds. In cardiac arrest, vasoactive agents are used to induce vasoconstriction
which increases total peripheral resistance and BP. Through various mechanisms, most notably the adrenergic receptors found on the vasculature of most tissues throughout the body, vasoactive compounds have been considered an integral part of resuscitation since at least 1894 when “adrenal gland extracts” were used to revive isolated heart preparations. The vasoactive pharmaceuticals involved during resuscitation are vasopressin and epinephrine.

Vasopressin, in conjunction with epinephrine, was for a time considered to be a promising therapy in the treatment of SCA. Vasopressin activates the V1 receptor in vascular smooth muscle which induces vasoconstriction and has been shown to potentiate endogenous catecholamines. In 2000, it was said that vasopressin, “may be a more effective pressor agent than epinephrine for promoting the return of spontaneous circulation in cardiac arrest.” The evidence from prospective clinical trials in humans is limited but consistently positive. Porcine models demonstrated increases in both coronary and cerebral perfusion pressure, leading to a belief that this would produce a concomitant increase in survival. Thus far, however, studies have demonstrated mixed results while ultimately concluding that there is no improvement in long-term survival following the use of vasopressin. As more and more data has been produced, the foundation supporting the use of vasopressin has eroded. For the 2015 ACLS (See Appendix B - Figure 6) and ERC ALS algorithms Vasopressin has been removed, citing no harms but no data suggesting improvement in outcomes. The unexpectedly poor results have been explained due to a reflexive increase in vagal tone, which may in fact be deleterious and there appears to be little overall change in cardiac output.
The most contentious debate surrounding ACLS pharmacotherapy is that of routine administration of epinephrine in cardiac arrest. During ACLS management of OHCA, epinephrine is the standard medication administered during cardiac arrest, given every three to five minutes.\(^2^9\) Epinephrine, or adrenaline, is a naturally produced adrenergic agonist and is the best studied vasoactive compound for the treatment of OHCA.\(^4\),\(^3^2\) Epinephrine has high affinity for all four major adrenergic receptors. \(\alpha_1\) receptors predominate in arterial walls.\(^4\),\(^3^2\) \(\alpha_1\)-adrenergic stimulation is linked to a G protein coupled receptor (GPCR), specifically the \(G_q\) protein, which activates Phospholipase C, leading to production of inositol triphosphate (IP3) and diacylglycerol (DAG).\(^1^0^2\) IP3 triggers \(Ca^{2+}\) release and DAG enhances activity of Protein kinase C (PKC) (See Appendix B - Figure 7 for Mechanism).\(^1^0^2\) In vascular smooth muscle, PKC activates proteins which have a net result of vasoconstriction.\(^1^0^2\) \(\beta_1\) receptors predominate in cardiac tissue and \(\beta_1\) activation increases HR via the SA node and myocardial contractility by acting in the walls of both atria and ventricles.\(^4\),\(^3^2\) \(\beta\) adrenergic receptors function via the \(G_s\) protein to trigger the adenylyl cyclase system which increases concentrations of cyclic AMP (cAMP) which triggers a second messenger cascade (See Appendix B - Figure 7 for Mechanism).\(^1^0^2\) \(\beta_2\) (predominantly in bronchi) and \(\alpha_2\) receptors (predominantly in the central nervous system) are less important in the treatment of cardiac arrest.\(^4\),\(^3^2\)

Animal models of cardiac arrest show that epinephrine use produces improvement in coronary and cerebral perfusion but human results have varied.\(^7\),\(^1^0^1\) Evidence of dysrhythmia and inhibition of cerebral microcirculation, as well as increased myocardial
O₂ consumption help explain the mixed results. Furthermore, excessive catecholamines can cause myocardial band necrosis, cytosolic hypercalcemia which leads to cardiac dysfunction including dysrhythmia, and splanchnic vasoconstriction. These potential side effects, plus the increase in O₂ consumption induced by the β1 receptor activation seem to negate the benefits of epinephrine in cardiac arrest.

Though not well understood at this time, some data suggests that epinephrine administration may be time sensitive. Ewy and Bobrow noted that while human data on epinephrine improving survival has not matched that seen in rats, on average rats received epinephrine 9 minutes post-arrest while humans received epinephrine 20 minutes post-arrest. Other studies by Ono et al. found that epinephrine did improve survival in a particular subset: those patients in whom CPR was performed for between fifteen and nineteen minutes.

Extensive studies assessing human data have shown that epinephrine significantly increases ROSC. This increase in ROSC has not, however, translated to an increase in overall survival. Administration of epinephrine during CPR has been shown by multiple studies to triple the likelihood of ROSC. Despite this increase, work by Bartos et al. has showed not only a reciprocal increase in mortality after admission to the ICU, but an overall decrease in survival to discharge. Dumas et al. assessed OHCA data from a large Parisian hospital and found an epinephrine dose-dependent decrease in survival. Individuals who received a greater dose of epinephrine, in general, had poorer overall outcomes than those who received no epinephrine or a smaller dose.
As it stands, data suggests that epinephrine should be limited to obtaining ROSC with the minimum dose used to accomplish this end. This remains contentious amongst healthcare providers who argue that without ROSC there is no chance of survival. These providers argue that the improvement of ROSC means that up and coming advances in post resuscitation therapies could make a difference now or in the relatively near future. What these providers fail to take into account is the fact that patients treated with epinephrine during resuscitation survive to discharge at a substantially reduced rate as compared to those who achieved ROSC without epinephrine. There is not, at present, any intervention which can correct for the detrimental effects of epinephrine administration during cardiac arrest.

Reversible cardiac arrest most often results from a significant alteration of the natural rhythm of the heart. As such, it has been the practice for many years to pharmacologically convert and/or prevent dysrhythmia through the use of antiarrhythmic compounds. Despite this history of extensive use, no antiarrhythmic medication was shown to have an overall increase in survival. Magnesium, a longtime staple of resuscitation attempts, has been shown to be useful only in the treatment of suspected hypomagnesemia-derived Torsades de point. Lidocaine, a long-used Na\(^+\) channel blocker, also shows no benefit in cardiac arrest, with no statistical difference between Lidocaine and placebo in cardiac arrest survival rates. The last of the commonly used antiarrhythmics for SCA is amiodarone. Amiodarone is structurally similar to thyroxine and is a potent antiarrhythmic which acts on multiple ion channels. There is some evidence of increased ROSC in the prehospital setting, but there is no evidence
suggesting improved outcomes. Extensive study has shown no overall increase in survival from OHCA to discharge related to the administration of amiodarone. Overall, across hundreds of studies by dozens of labs, groups, and organizations, there is no evidence that any antiarrhythmic drug improves survival or CPC.

The second major category of ALS intervention to be considered is advanced airway management. Advanced airway management of OHCA involves either ETI, which involves placement of a tube which connects directly from the opening of the oropharynx to the carina, or SGA which involves the blind insertion of a device which occludes the esophagus. ETI has been performed by paramedics and other ALS providers in the United States for more than thirty years. McMullan ETI has been the standard of care in the US for much of that time, with advanced airway management taking a priority in many incidents of OHCA. More recently, the SGA have come into vogue. Because they are inserted blindly, without the use of laryngoscope, they can be inserted more quickly and with less training required. These advantages have led to the belief amongst some ALS providers that SGA represent the way of the future, providing the benefits of ETI without some of the risks. Recent data, however, has suggested that not only do patients treated with ETI have better outcomes than those treated with SGA, but that patients without any advanced airway experience better outcomes than either ETI or SGA.

There is conflicting evidence relating to the timing of airway placement. Some studies have shown that earlier placement of an advanced airway correlates to improved survival while others have suggested that placement within the circulatory phase of arrest
was the key to improved outcomes.\textsuperscript{107, 110, 111} There are currently large scale randomized trials in the UK and Europe attempting to address the questions of timing, choice of advanced airway, and overall benefit of advanced airway intervention.\textsuperscript{111} Until these trials are completed, understanding of the use of ETI and SGA in the treatment of the OHCA remains unclear.

Delays in CPR, defibrillation, or ventilation due to placement of advanced airways have been observed in many studies and are generally believed to relate to poorer outcomes due to increased intermittent hypoxia during and/or between intubation attempts at advanced airway placement.\textsuperscript{76} The ERC goes so far as to recommend ETI only when it can be performed without any interruption of CPR, save for passing the tube through the vocal cords.\textsuperscript{23} Some studies have suggested that ETI increases intrathoracic pressure, reducing return of blood to the heart.\textsuperscript{76} Specific to the SGA, animal studies have shown decreased cerebral blood flow due to carotid artery occlusion as a result of SGA placement.\textsuperscript{111} Perhaps because of this induced cerebral hypoperfusion nearly every study has found superior outcomes in patients treated with ETI as compared to SGA, though Hasegawa et al. found no significant difference between ETI and SGA.\textsuperscript{109, 111}

The combination of these potential difficulties is believed to contribute to the observed decrease in survival in patients who had placement of an advanced airway during OHCA.\textsuperscript{56, 111} Initially reported by Hasegawa et al., CPR and rapid defibrillation with the use of BVM alone was found to have improved outcomes as compared to OHCA treated with an advanced airway.\textsuperscript{109} The Hasegawa study was criticized by McMullan et al.\textsuperscript{110} due to the relatively new nature of ETI in Japanese EMS, a factor which was self-
acknowledged in the study.\textsuperscript{109} While ALS providers have performed ETI for 30+ years in the US, it has been used for just over 10 years in Japan.\textsuperscript{110} Follow-up studies by McMullan et al. using the CARES registry have subsequently supported the results of Hasegawa et al. (“OHCA outcomes were markedly better among those who received no advanced airway interventions compared with those who received ETI or SGA.”).\textsuperscript{110} Conversely, McMullan et al. did find lack of an advanced airway was associated with an increase in other characteristics associated with positive outcomes (EMS-witnessed arrest, shockable rhythm, and arrest in public or healthcare location).\textsuperscript{110} Statistical manipulations using ANOVA, Chi square, Kruskal-Wallis tests, and a multivariate analysis maintained the superiority of BVM to advanced airway after isolation from potential confounds.\textsuperscript{110} The disruption that ALS care places on the resuscitation effort was not a consideration in any encountered study.\textsuperscript{111} Firefighters, Police officers and BLS providers tend to perform CPR while ALS providers perform invasive interventions. After placement of an advanced airway, the “30:2” sequence of CPR is no longer used, leading to continuous uninterrupted compressions by first responders with periodic ventilations by additional first responders or ALS providers.\textsuperscript{72} There is, however, sparse data describing the effect that this change in the more practiced 30:2 resuscitation has on the resuscitation dynamic. Since much of CPR training does not occur with an advanced airway, most EMS crews will have far more familiarity in CPR with a BVM, resulting in potential disruptions in rhythm and comfort.\textsuperscript{112}

The last component of ALS care in OHCA to be considered is the use of end tidal carbon dioxide ($E_tCO_2$) monitoring. $E_tCO_2$ monitoring measures the partial pressure of
the expired carbon dioxide. At fixed inspiratory volume (provided by BVM), in a low blood flow situation, $E_t\text{CO}_2$ is an indicator of pulmonary blood flow, and thus cardiac output, during CPR. $^{29,56} E_t\text{CO}_2$ is also a sensitive indicator of CPR quality and ROSC without need for invasive measurements and CPR stoppage for pulse checks respectively. $^{29} E_t\text{CO}_2$ waveform capnography (a visual, graphic representation of $E_t\text{CO}_2$) is a sensitive indicator of successful ETI and of tube dislodgement. $^{29,23,56,111} E_t\text{CO}_2$ can be used to identify errors and/or weak points in the resuscitation effort and the use of $E_t\text{CO}_2$ has been generally associated with improved ROSC and survival, suggesting better CPR and airway management. $^{56}$ The improvements in overall outcomes in $E_t\text{CO}_2$ measured OHCA are generally underpowered and are deserving of more extensive research. $^{56}$ In general, $E_t\text{CO}_2$ appears to be a powerful tool which can be used to provide data about ongoing resuscitation efforts, after action review of those efforts, and valuable physiological data. $^{56,111}$ These positives, combined with the more or less non-existent detracting factors, indicate that $E_t\text{CO}_2$ monitoring should be increasingly used in OHCA. $^{7,29}$

Looking at ALS treatment as a whole, many studies have sought to determine whether BLS or ALS-treated patients fare better. Bakalos et al., in a meta-analysis of ALS-BLS comparative studies, showed a 47% increase in survival amongst patients treated by ALS as compared to BLS. $^{27}$ Other studies have shown approximately equal outcomes for BLS and ALS-treated victims of OHCA, $^{28}$ while Stiell et al. $^{113}$ have showed an overall decrease in survival for patients treated with ALS interventions (See Appendix A - Table 5 for Stiell’s Data). $^{28,113}$ Likewise, a survey conducted by Medicare found
BLS-treated OHCA had better survival to discharge than ALS. Bakalos et al’s analysis aside, the literature suggests that patients who received ACLS care with IV access and medication administration had better short term survival but had increased ROSC, with no difference in survival to discharge.\textsuperscript{105, 113}

More than ten years prior to this writing, Isenberg and Bissel firmly suggested that ALS provides no benefit with regard to improved outcomes in the care of OHCA.\textsuperscript{31} Their meta-analysis of research described time to defibrillation and early initiation of CPR as the critical factors in resuscitation, concluding “ALS does not benefit patients in cardiac arrest beyond early defibrillation and CPR.”\textsuperscript{31} In the ACLS guidelines for 2010, Neumar et al. concluded that IV access was not necessarily useful and that improving quality of CPR should consistently remain the focus of resuscitation efforts.\textsuperscript{7, 76} E\textsubscript{r}CO\textsubscript{2} detection remains the only technology employed by ALS providers shown to improve resuscitation efforts.\textsuperscript{76}

\textit{Early Post-Resuscitative Care}

While intra-arrest use of ALS has shown little if any benefit, post-ROSC care can indeed be improved by the use of ALS interventions. While the greatest portion of cardiac arrest victims die from the initial cardiac arrest (less than 18\% of all cardiac arrest victims achieve ROSC) successful ROSC is just the beginning of the recovery process.\textsuperscript{113} As mentioned previously, the metabolic dysfunction induced by cardiac arrest itself, and I/R injury immediately post-arrest, are significant contributors to OHCA morbidity and mortality.\textsuperscript{43, 46} Biological death (brain and multiorgan death, as opposed to cessation of
heartbeat) soon after ROSC is generally due to hemodynamic dysfunction, resulting from myocardial stunning, and is generally transient with recovery of function by 72 hours (See Appendix B - Figure 4). Later biological death is most often related to post-anoxic neurological consequences. The goals of post-resuscitative care are: 1) Assessment and stabilization of cardiopulmonary status, 2) Determining etiology of arrest, 3) Neuroprotection, and 4) Preventing recurrence of arrest.

Historically, resuscitation of any kind involved the administration of high flow oxygen (10, 15 or even 20 L/min via NRB). In hypoxic situations, cell signaling begins triggering apoptosis. It is now believed that high flow oxygen therapy and unrestrained attempts to increase the blood pressure of the patient actually increase infarct size.

Titration to a set SpO₂ range has been shown to improve outcomes for patients with ROSC. Though not explicitly defined at this time, a SpO₂ range of 94 to 98% has been proposed as optimal. Hyperoxic damage has been shown to be dose dependent, suggesting that, rather than keeping SpO₂ below a given threshold (i.e. not 100% oxyhemoglobin saturation) it may be best simply to maintain it as low as can be determined to be safe. However, noninvasive measurement of SpO₂ in cardiac arrest is not nearly as accurate as arterial monitoring of BP and SpO₂, which is rarely performed OOH. Supplemental oxygen-induced myocardial injury in STEMI patients is well documented and can be easily avoided.

Maintaining proper ventilation has also been identified as a source of improved survival. While potentially harmful during resuscitation, post-resuscitation intubation for
airway protection and ventilation maintenance has shown some benefit. Hypocarbia, abnormally low levels of CO₂ typically caused by hyperventilation, has been shown to cause cerebral vasoconstriction and shunting of blood away from the brain, resulting in further ischemic injury. Hypercarbia, abnormally high levels of CO₂ typically caused by hypoventilation, has also been shown to adversely affect survival, increasing neurological and cardiac damage. Given this, maintaining normocarbia is currently considered the best approach for post-resuscitative ventilation.

Maintaining BP, particularly MAP, and CO in post-resuscitation is critical to positive outcomes. Higher MAP is associated with higher cerebral perfusion pressure, and thus improved neurological outcomes. Systolic BP between 90 and 100 is the currently advised goal. There is as yet no agreed upon optimized MAP and it is possible that different arrest etiologies may have different ideal MAPs (ex. a patient with significant damage due to infarct may be better served by a low MAP to avoid overtaxing the heart). As it stands, CO and BP can be improved via IV support (pharmacological aid and fluid resuscitation) as well as intra-aortic balloon counterpulsation and revascularization. Due to the limitations of the OOH setting, only IV support is feasible for immediate post-ROSC care in OHCA.

The goal of IV support is to restore perfusion until myocardial stunning and transient inhibition of cerebral autoregulation has abated. The initial treatment of post-ROSC hypotension is filling of the right heart, which is preferentially accomplished through volume expansion via IV. All pharmacological therapies have side effects and in the absence of a critical need for pharmacotherapy, IV fluids alone are preferred.
While there are three classes of drugs, catecholamines, phosphodiesterase-III (PDE) inhibitors and calcium sensitizers, commonly used to maintain post-resuscitation hemodynamic stability, only catecholamines are commonly used in the OOH setting and thus only catecholamines will be discussed herein. Catecholamines act on post-synaptic terminals and activate sympathetic receptors. Pharmaceuticals that work via catecholamine systems can directly activate receptors, change metabolism of endogenous catecholamines or change production of endogenous catecholamines. Catecholamines have a variety of chronotropic (rate altering), inotropic (contractility altering), and/or vasoactive properties.

Prolonged tachycardia has been associated with poorer outcomes during post-resuscitation and thus drugs with strong chronotropic activity should be avoided in most cases. However, because significant bradycardia is also associated with poorer survival it is important to have a chronotropic drug available. Because myocardial stunning leads to reduced cardiac output, inotropes and vasoconstrictors are necessary to maintain BP. Norepinephrine is a potent α1 agonist, inducing significant vasoconstriction with “modest” β1 activity leading to a small increase in CO. Dobutamine is a synthetic catecholamine with high affinity for the β1 receptor producing high inotropic activity with minimal chronotropic activity, making it an attractive option for cardiogenic shock. Dopamine acts widely on both α and β receptors as well as dopamine-specific receptors (See Appendix B - Figure 7 for mechanism). Intermediate doses of dopamine have been shown to increase CO as well as have a modest vasoconstrictive effect, though there is a higher risk of dysrhythmia and splanchnic vasoconstriction.
The combination of norepinephrine and dobutamine has been suggested as the ideal combination for hemodynamic stabilization due to the inotropic increase (dobutamine) to address cardiogenic shock combined with the increased vasoconstriction (norepinephrine) reversing vasodilation due to inflammation.\textsuperscript{34} While there is no firm consensus, the two are the most studied pharmaceuticals and data suggests the best outcomes result from some combination of the two.\textsuperscript{34,51} Others have suggested a condition-based system with norepinephrine used for severe cardiogenic shock (systolic BP <70) or dobutamine and/or dopamine for moderate shock (BP 70 to 100).\textsuperscript{32}

Therapeutic hypothermia (TH) also known as Targeted Temperature Management (TTM) has been shown to be the only procedure which effectively improves survival to discharge with good neurological outcome in comatose patients who experience ROSC.\textsuperscript{34,123,124,125} Within 20 seconds of anoxia the O\textsubscript{2} stores of the brain are depleted and within 5 minutes post arrest there is an almost complete absence of both glucose and ATP.\textsuperscript{126} Gaieski et al. describe the approach of TTM as treating post-resuscitation syndrome in a manner similar to sepsis.\textsuperscript{124} Looking at the post-arrest state as a widespread inflammatory response to insult appears to have merit in developing strategies to reduce overall morbidity and mortality (MM).\textsuperscript{124} Hypothermia reduces inflammation, apoptosis, and necrosis, resulting in an overall reduction in I/R injury.\textsuperscript{126,127} TTM is thought to function, in part, by reducing cerebral demand for oxygen, with some researchers citing as much as a 10\% reduction in cerebral metabolism per degree Celsius drop in core temperature.\textsuperscript{127} Though this dose-dependent change in metabolism has been reported by several sources,
extensive study has shown no significant difference in survival observed between TTM to 34°C as opposed to 36°C.127

The brain is particularly sensitive to derangements in ion concentrations, protein alteration, and modification of other biological molecules.126 The exquisite sensitivity of brain tissue is likely the major cause of late post-anoxic neurological complications.127 TTM slows metabolism and helps reduce toxic metabolites.123,127 TTM has also been shown to reduce cellular excitation via Ca²⁺ and glutamate.51,123 Data robustly supports TH for shockable rhythms with Maznyczka and Gershlick127 reporting a “20% relative reduction in mortality” and Truong et al.52 showing data for improved neurological status by up to 100%.52,124,127 While data for non-shockable rhythms has typically been viewed as less conclusive, Sung et al reported a nearly 300% improvement in good neurological outcome at discharge (5% to 14%) in their review of OHCA with TH in Los Angeles county.128

Data on timing of TTM has been somewhat controversial, particularly with regard to initiation of TH by EMS. There has been a time dependent observation noted in animal models of cardiac arrest, but human data has failed to reproduce this trend.129 The cause of this was initially believed to be a failure in the OOH setting to produce a meaningful change in core temperature, but subsequent studies which confirmed meaningful change in temperature still noted no difference in survival for EMS or hospital initiated TTM.125,129 Subsequent study on TH as it related to “time down” for victims of cardiac arrest demonstrated the greatest improvement in outcomes in those down greater than 10 minutes (the metabolic phase of cardiac arrest described by Weisfeldt and Becker).2,6,123
Furthermore, while there are notable benefits to TTM for improvement of survival post cardiac arrest, there are notable harms to the process.\textsuperscript{51, 127} Studies have shown increased rates of pulmonary edema, arrhythmias, diastolic dysfunction and prothrombic effects due to reduced core body temperature.\textsuperscript{33, 34, 127} All of these factors are known to contribute to MM from cardiac arrest and increase the risk of a subsequent arrest.\textsuperscript{33, 34, 118, 127} These potentially life-threatening complications, and the limited OOH resources for addressing them, may be a part of why prehospital initiation of TTM has shown no benefit.\textsuperscript{33} As a whole it has been shown for the majority of SCA, of presumed cardiac origin, that there is no benefit to field initiation of TTM.\textsuperscript{116, 130} However, due to the urban nature of much of the research on OOH initiated TH, it is difficult to say whether or not there might be a length of transport for which initiation of TH might outweigh the obvious risks.\textsuperscript{125} As it stands, transport to a center capable of initiating TTM is coming into vogue with the AHA beginning to recommend “regional centers for post-resuscitation care.”\textsuperscript{126} Much like the concept of stroke, trauma, and STEMI centers, the idea of post-resuscitation centers looks to potentially save many lives each year as well as improve neurological outcomes.\textsuperscript{120, 126} In a pilot study of sorts, transport to a designated cardiac arrest center was associated with an improved rate of survival.\textsuperscript{26} Overall, there was an increase in survival from 9 to 14% for patients transported to a dedicated center.\textsuperscript{52}

Preventing further cardiac arrest can be exceedingly difficult depending on the cause of the initial arrest. Coronary reperfusion at a hospital with coronary angiography and/or open heart bypass is the only solution for a severe occlusion of the coronary arteries and there is minimal ability to assess electrolyte levels in the prehospital setting.\textsuperscript{7}. 
In a study where 77% of OHCA patients with presumed cardiac etiology underwent catheterization, 97% had Coronary Artery Disease (CAD) and greater than 80% had a major coronary artery occlusion. In the case of these particular causes of OHCA there is also no evidence supporting the use of prophylactic antiarrhythmics to prevent recurrence.
DISCUSSION

Pathophysiology of Cardiac Arrest

The field of resuscitation research has grown substantially in the last decade. We now have a better understanding of the process the body endures following SCA. The three phase model of cardiac arrest currently provides the most comprehensive explanation of what happens to the body in the minutes after SCA (See Appendix A - Table 3 for Summary). Cardiac arrests in the electrical phase should receive immediate defibrillation. Even under ideal conditions, it remains difficult to firmly place a victim of SCA in one of the three phases, as previously outlined in the Pathophysiology section of Review and Analysis of Published Studies (Page 9). In the OOH, with the high likelihood of unwitnessed arrest it can be more difficult to determine time since SCA. Witnessed cardiac arrests with rapid EMS response should be considered to be in the electrical phase and should thus be defibrillated immediately. Unwitnessed cardiac arrests should be presumed to be in the circulatory phase and 2 minutes of CPR should be performed prior to defibrillation. As such, it is reasonable to suggest that non-witnessed cardiac arrests should undergo CPR prior to defibrillation, as should any cardiac arrest with a delayed response time (greater than 5 minutes). Due to the high probability that first responders will encounter a cardiac arrest in the circulatory phase, research on therapeutics tailored to that phase, as well as research designed to improve the understanding of how best to treat arrests during that phase (is 90 seconds of CPR sufficient, is 3 minutes ideal?, etc.). Cardiac arrests in the metabolic phase have
little chance of resuscitation and further research is needed to identify potential metabolic and cellular level therapeutics which may be able to help in survival in this phase.\textsuperscript{6,42}

The greatest detriment to treatment in accordance with the three phase model of cardiac arrest is the difficulty of phase identification.\textsuperscript{6} More research into ECG waveform analysis, prehospital lactic acid levels, or arterial pH levels may help; however, identifying critical markers for each stage is needed before stage-directed treatment can become the standard of care.\textsuperscript{6}

Prompt reperfusion of tissue, via angiography, coronary bypass or other interventions is still essential to the treatment of many OHCA, particularly those caused by STEMI.\textsuperscript{7,29,57} Transport to a center capable of these procedures is necessary for survival in many cases.\textsuperscript{26,52} Due to the significance of I/R injury it appears that reduction of ROS is necessary for improving overall survival.\textsuperscript{8,9,45-48} Supplemental oxygen should be kept to an absolute minimum and SpO\textsubscript{2} should be used in the prehospital setting to titrate supplemental oxygen.\textsuperscript{117,118} Excessive use of oxygen leads to poorer outcomes due to ROS generation and while a number of therapies to deal with ROS have been proposed and studied, none are both sufficiently well understood and feasible in the prehospital setting.\textsuperscript{119} The need to control the systemic inflammatory response, particularly neutrophil activation, has largely gone unnoticed and no therapies save for TTM have been shown to have any benefit in controlling this inflammatory process.\textsuperscript{6,9,10,46,43}

The future of resuscitation science hinges on improving our knowledge regarding the pathophysiology of OHCA. Research is needed to identify ideal values for vital signs like SpO\textsubscript{2}, MAP and HR, and $E\text{TCO}_2$.\textsuperscript{7} Better understanding of ideal ranges for these vital
signs as well as lab values during arrest and immediately afterward could dramatically improve our understanding of the approach needed for specific arrest etiologies and for SCA in general.\textsuperscript{7, 51, 118, 34, 32}

\textit{Regional Variation}

While it is widely accepted that there is a drastic, unacceptable, degree of variation in OHCA survival across the US, the reasons behind it remain elusive.\textsuperscript{12, 13, 17} One of the major reasons for this is the failure to collate and communicate cardiac arrest data.\textsuperscript{1, 7} The answer to this failure to communicate appears to be a lack of databases. A national cardiac arrest database would allow for better post-hoc analysis of cardiac arrests. Furthermore, reporting of OHCA data is currently voluntary leading to a likely selection bias.\textsuperscript{7} Though most researchers now follow the Utstein guidelines [discussed in the Utstein section of Review and Analysis of Published Studies (Page 8)], there remain differences in reporting data which makes comparison difficult.\textsuperscript{1, 7, 14, 132} These differences make it exceedingly difficult to identify practices in a region which may be problematic or superlative.\textsuperscript{1, 7} Wide variation in data collection, reporting and interpretation also leads to difficulties in dissemination of best practices.\textsuperscript{1, 7} Critical variables need to be incorporated into a mandatory national (or at least robust regional) database which answers to a governing body of some form (such as the CDC).\textsuperscript{1, 7}

While databases are key to identifying sources of regional variation, there are some smaller changes which can lead to improvement in variation between regions without as substantial a financial burden. Proper understanding of resource availability,
particularly in rural locales where transport to a tertiary care center involves significant
time and/or distance, is essential to improving outcomes. Understanding which sites are
capable of TH, coronary angiography, or coronary bypass procedures aids in the decision
of where to transport critical patients of OHCA. 52, 120, 126 Those patients who have
achieved ROSC need exceptional post-resuscitative care, and identifying regional cardiac
arrest centers can be a first step in moving toward a more uniform care of the OHCA
victim. 1, 52, 120, 126

Chain of Survival

The Chain of Survival is an effective description of the necessary steps in the
successful treatment of OHCA. 37 Early Recognition, Early CPR, Early Defibrillation,
Early ALS Care, and Early Post-Resuscitative Care are the essential components required
for a successful OHCA resuscitation. A combination of Early ALS Care and Early Post-
Resuscitation Care would be a reasonable streamlining of the Chain of Survival. 23, 28, 105,
113 There is, however, a particular aspect that must be made clear in the treatment of
OHCA. The factors which have been shown to significantly improve outcomes in
OHCA: 1) Bystander witnessed SCA, 2) EMS witnessed SCA, 3) Bystander CPR, 4)
VF/VT as presenting rhythm, and 5) Prehospital ROSC must be made points of emphasis
in conjunction with the chain of survival as currently constituted. 15

Early Recognition

Substantive improvements in the recognition of cardiac arrest can easily be made.
An effort should be made by hospitals and physicians to educate patients at substantial
risk of SCA (elderly, hypertensive, hypercholesterolemic, diabetic) and those in close contact with these patients (caregivers and family members) about the various signs and symptoms that can precede a cardiac event.\textsuperscript{1, 7} The caregivers and family members should also be trained in how to recognize SCA should it occur.\textsuperscript{1, 7} Early detection of critical precipitating events of OHCA are essential to improving the percentage of OHCA witnessed, and preventing OHCA.\textsuperscript{16, 17, 131} Early recognition is a low cost high yield approach which is likely to make some difference even though the signs and symptoms are varied and are not guaranteed to present prior to SCA.\textsuperscript{17}

The area of paramount concern for the early recognition of OHCA is the relationship between dispatcher and 911 caller.\textsuperscript{7, 57} With two simple questions: 1) ”Is the victim responsive or conscious?” and 2) “Is the victim breathing normally?”, cardiac arrest can be identified with high sensitivity and specificity.\textsuperscript{1, 52} The occurrence of agonal respirations are an important confounder to the identification of cardiac arrest and thus all emergency professionals, dispatchers, and persons likely to encounter SCA should be familiar with agonal respirations.\textsuperscript{1, 20, 52} All 911 dispatch centers should have a policy in place for DaCPR and specific DaCPR training should be encouraged.\textsuperscript{1, 7, 20} DaCPR increases the likelihood of a bystander performing CPR and thus improves overall survival from OHCA.\textsuperscript{1, 7, 57} Aggressive CQI should be conducted to ensure consistent improvement of resuscitation efforts involving DaCPR.\textsuperscript{7, 20} Immediate dispatching of the nearest defibrillator equipped unit is also essential to early recognition and treatment of suspected cardiac arrest. Multi-tiered dispatching involving Police, Fire and the closest
available EMS gives the best chance for early arrival and early initiation of CPR and Defibrillation, and thus the highest chance of survival.\textsuperscript{35, 55}

Technological advances can also be helpful in improving response time to victims of OHCA. A number of commercial devices make use of traffic signal preemption to change lights favorably for responding emergency vehicles, clearing congestion and leading to reduced response times.\textsuperscript{62, 63, 74} Traffic signal preemption has been shown in multiple studies to not only reduce response times of emergency vehicles but also to reduce incidence of emergency vehicle collisions suffered at TSP-equipped intersections.\textsuperscript{62} Reduction of response times by approximately 1 min (as described in both US and Japanese studies) could lead to an improvement in OHCA survival by up to 10\%.\textsuperscript{52, 62, 63} Reported costs of implementation are limited, with a large US study reporting costs of approximately $6,000/signal and $1,500/emergency vehicle (rounded averages taken from 2006 study).\textsuperscript{62} TSP devices can also be used to allow a reduced number of units to cover a fixed area in a given time, reducing costs to emergency vehicle operation.\textsuperscript{62} Though the data is promising, the only large study found (for the US) was published in 2006.\textsuperscript{62} Subsequent, up to date research, could do much to improve our understanding of the value of TSP.\textsuperscript{62}

Social media in conjunction with mobile phones has been shown to be promising for recruiting lay rescuers to the site of cardiac arrests.\textsuperscript{7, 52} The Pulse Point Foundation in California performed trials where smart phones were used to identify local AEDs and direct self-selected CPR-trained bystanders to the location of cardiac arrests.\textsuperscript{7} While data regarding outcomes of patients who received assistance via this method is unavailable,
the study demonstrates the feasibility of the concept. Similar studies in the Netherlands and Sweden have also demonstrated improvements in bystander CPR rates using mobile phone technology. In conjunction, comprehensive education of high risk patients and caregivers along with proper training for 911 dispatchers, and utilization of new technologies can greatly improve recognition and decrease response times to victims of OHCA.

**Early CPR and Defibrillation**

In accordance with the guidelines for early recognition, the most important factor in improving time to early CPR is a continued, and growing, emphasis on bystander CPR. A substantial difference can be made by improving the percentage of bystanders comfortable with performing CPR. A significant factor in that improvement is recognizing the fear that the idea of mouth-to-mouth resuscitation carries. An emphasis on compressions-only CPR for bystanders has been shown to improve rates of bystander CPR and overall patient outcomes. As mentioned earlier, DaCPR is a highly effective method of increasing the likelihood of bystander CPR and thus improving the likelihood of a victim receiving Early CPR.

At the same time, a targeted approach to CPR training must be initiated to focus on traditionally underserved communities. Neighborhoods which are majority black and/or Hispanic as well as rural and low income communities have the lowest rates of CPR training and often have higher than average rates of SCA. The limited EMS access
in these communities, particularly in rural and some urban settings, leads to poorer outcomes. These poor outcomes can be offset somewhat by targeted training of CPR for the family and caregivers of patients at high risk of SCA (as previously outlined). Efforts should be made to defray the costs of CPR training at the community level, as well as to publicize Spanish language CPR which is offered in many areas by the AHA and/or the Red Cross. Online CPR courses with subsequent skill verification shows similar efficacy at a reduced cost. Incorporating CPR and AED training into schools serves to provide training across all races and socioeconomic statuses as well as to promote better learning of the material due to teaching in an environment already conditioned for learning. In a similar vein, Japan, Denmark and a number of other countries require CPR and/or First Aid training in order to obtain a driver’s license. These countries, in general, have better rates of bystander performance of CPR than the US.

Some evidence demonstrates that initial CPR training remains effective for approximately one year. Self-selecting volunteers who are at high likelihood of encountering OHCA should be trained annually to keep skills up to date. Training with new technology such as rhythm strip recorders and compression force sensors can increase the overall cost of training but should be considered with professional rescuers to enhance understanding of proper CPR amongst the persons most likely to perform it on a regular basis. Studies focusing on the efficacy of these new technologies on CPR performance should be performed to confirm the cost/benefit of these technologies. During CPR, real-time feedback, through AEDs or through adjuncts like E\textsubscript{2}CO\textsubscript{2} have
been shown to improve CPR by providing real-time assessment of CPR quality, showing rescuers when they should switch and ensuring proper depth and rates of compressions.\textsuperscript{1, 87, 135} Devices such as metronomes are also effective at maintaining proper compression rates.\textsuperscript{76, 77, 79}

Research continues on the proper rate and depth of compressions, but at the time of this publishing a rate of between 100 and 120 compressions per minute at a depth of between 5 and 6 cm (2-2.4 inches) is recommended.\textsuperscript{7, 72} BVM ventilations should be just enough to allow for chest rise and hyperventilation should be avoided.\textsuperscript{7, 72} Hyperventilation decreases systemic oxygenation by lowering coronary perfusion pressure and increasing intrathoracic pressure.\textsuperscript{7} There is positive data suggesting that passive insufflation via an OPA and NRB is effective for witnessed arrests and can thus be considered.\textsuperscript{72, 77} There is insufficient evidence at this time to recommend the routine use of passive O\textsubscript{2} insufflation in all cases.\textsuperscript{72}

Mechanical CPR should be avoided unless there is a risk to the rescuers (such as in a moving ambulance) or where manual CPR would be too unwieldy to be effective (such as a prolonged extrication or carrying down stairs).\textsuperscript{17, 56, 57, 94} When possible, manual CPR should be performed. ACD-ITD devices have shown positive results in some tests when used as an adjunct to manual CPR.\textsuperscript{41, 73, 90, 96, 98} The modest improvement in results, and the high cost of large scale transition to use, makes ACD-ITD impractical as a general recommendation but it remains an intriguing possibility.\textsuperscript{23, 72}

The absolute importance of defibrillation must remain paramount in an understanding of cardiac arrest pathophysiology and treatment.\textsuperscript{1, 16, 17, 20, 39, 52, 54, 64, 131}
While early CPR staves off biological death, and can be useful in making VF waveforms coarser, defibrillation is needed to convert a non-perfusing rhythm.\textsuperscript{1, 41} Particularly in rural areas, AED deployment in police cars should be considered to reduce time to defibrillation.\textsuperscript{7} AEDs should be registered with 911 dispatch so that SCA that occur in a location with a nearby AED can be identified.\textsuperscript{1, 7} The formulation of an AED registry, whether at the national, state, or even city level could be effective in improving bystander use of AED.\textsuperscript{7, 74} AEDs expected to be used by lay rescuers should also be programmed with compression-only CPR instructions. Further use of PAD should be encouraged as AEDs consistently become cheaper and more widely available.

At an organizational level, all calls where CPR is administered or an AED is deployed should be subject to review for CQI.\textsuperscript{1, 7, 26} AED data (and voice recordings if possible), dispatch recordings, and PCRs should be utilized to assess strengths and weaknesses in the chain of survival in each and every OHCA.\textsuperscript{1, 7} By identifying the issues experienced with calls each organization and, through databases, resuscitation researchers can identify the causes of delays and issues which impede care. Unless errors are particularly egregious, CQI should not be an area for reprimand of providers but rather for improvement; as the name suggests.\textsuperscript{1}

Benefit may be gained from future research focusing on cementing our understanding of vital signs and laboratory values [See Pathophysiology recommendations in Discussion (Page 46)], as well as improving our understanding of passive O\textsubscript{2} insufflation.
Early ALS

The essential ALS components of IV administration of medications, advanced airway management, and E₄CO₂ have long been considered to be the standard of care for OHCA despite the fact that none of these interventions are associated with improved survival.²³,²⁸,¹⁰⁵,¹¹³

IV medications are the core of ACLS resuscitation. The first medication to be administered in the ACLS algorithm (See Appendix B - Figure 6) is epinephrine. Epinephrine, or adrenaline, has been used for years in resuscitation.¹,⁷,²³,²⁹,¹⁰¹ The cardiac excitation and peripheral vasoconstriction caused by epinephrine leads to a substantial increase in ROSC.¹⁰⁰,¹⁰¹,¹⁰⁵,¹¹³ Despite this increase in ROSC, there is no increase in overall survival following administration of epinephrine.³¹,¹⁰¹ There is, in fact, an increased fraction of post-ROSC patients who die following epinephrine treatment overcoming the benefits of increased ROSC.²⁹,¹⁰⁴,¹⁰⁵ A time-sensitive model of epinephrine has shown potentially improved survival but the data is inconclusive at this time.⁶⁵ Because of the preponderance of evidence, it is reasonable at this time to recommend against the routine use of epinephrine for the treatment of OHCA.⁵⁶

Vasopressin was previously used in conjunction with epinephrine as a therapy to increase blood pressure and increase ROSC.²⁹,¹⁰⁰ No increase in survival has been identified with the use of vasopressin and it has been removed from ACLS protocols for that reason.²⁹

Conversion of arrhythmias to stable rhythms via antiarrhythmic medication marks the other main component of ACLS pharmacology. There is no compelling
evidence to suggest that the use of any antiarrhythmic, be it amiodarone or lidocaine, improves survival when administered intra-arrest.7, 29, 106, 76, 100 Because of this, there is no reason to administer antiarrhythmic medications during cardiac arrest.7, 29, 76, 100, 106,113 The dearth of evidence supporting either major category of pharmacological adjunct during cardiac arrest suggests that IV access should, in fact, be delayed until ROSC.29, 76, 113

Another major area of ALS care is the advanced airway. Neither the technically complex ETI, nor the simpler blind insertion of a SGA has been shown to improve outcomes in OHCA.108-110 Use of a BVM during cardiac arrest has been shown to improve outcomes as compared to advanced airways.109 Because of the lack of evidence to support placement of an advanced airway, as well as the delay in CPR needed to perform the intervention, placement of an advanced airway should be delayed until after ROSC has been achieved.33, 51, 111

The singular ALS intervention which is currently associated with improved survival from OHCA is one that itself has no effect on the patient.23 E\textsubscript{t}CO\textsubscript{2} measures are indicative of successful compressions and ventilations and are typically used via an advanced airway with an ALS cardiac monitor.29 Advances in E\textsubscript{t}CO\textsubscript{2} monitoring for use at the BLS level in the near future may mitigate even that singular benefit ALS has in OHCA.

Invasive, intra-arrest, ALS interventions have not been shown, in any randomized clinical trial, to improve cardiac arrest survival.29 Because of this, it seems reasonable to suggest that the nearest ambulance respond to a cardiac arrest, regardless of level of care,
along with fire and police as discussed previously in the *Early Recognition* section of *Review and Analysis of Published Studies* (Page 20).

With improvements, and cost reductions, in this technology, it is not farfetched to assume that BLS use of E\textsubscript{5}CO\textsubscript{2} in the near future could seriously draw into question the need for ALS providers during active cardiac arrest.

**Early Post-Resuscitative Care**

While treatment of cardiac arrest itself should not be delayed for ALS care, post-ROSC, ALS can make a substantial difference in survival and overall quality of outcome.\textsuperscript{33, 44, 51, 52 111, 115, 116, 126, 130} It is well established that supplemental O\textsubscript{2} increases the size of infarct in STEMI and generates significant ROS which contribute to I/R injury.\textsuperscript{7, 46, 118, 119} Thus, of primary importance should be the *limited* use of supplemental O\textsubscript{2} to titrate SpO\textsubscript{2} to between 94 and 98%; however, the ideal range is not yet known, and further research must be conducted to establish that range.\textsuperscript{38, 118} Early death after ROSC is primarily due to hemodynamic instability.\textsuperscript{44} IV fluids and pharmacological support are essential in the post-resuscitative care of many OHCA.\textsuperscript{33, 34} Research has shown that prolonged tachycardia should be avoided in post-resuscitative care as well as the fact that significant bradycardia also contributes to poorer survival.\textsuperscript{32, 34, 51, 115} Dobutamine has been shown to be effective at increasing inotropy with minimal effect on chronotropy, with data suggesting it is theoretically ideal for post-resuscitative care.\textsuperscript{34, 51} In patients with more severe hypotension, norepinephrine (to induce systemic vasoconstriction) in conjunction with dobutamine (to increase CO) appears to be an effective combination due
to the increase in vascular resistance achieved in conjunction with the increased cardiac contractility.\textsuperscript{32, 51} Goal-directed therapies should be the standard of care with target values for MAP, SpO\textsubscript{2}, E\textsubscript{t}CO\textsubscript{2} and HR placed within an algorithm.\textsuperscript{118} All of these values remain inexact at the time of this writing but research is helping to elucidate specific recommendations. While advanced airway placement was not associated with improved survival intra-arrest, post-ROSC advanced airway management has been associated with better survival.\textsuperscript{33} Advanced airways have been shown to reduce intracranial pressure and to aid in management of SpO\textsubscript{2} and E\textsubscript{t}CO\textsubscript{2}.\textsuperscript{33, 76} Because of these improvements, advanced airway management should be performed in patients who remain unconscious post-ROSC.\textsuperscript{33, 51} Maintaining normocarbia via artificial ventilation, particularly in conjunction with an advanced airway, should be considered a priority in post-resuscitative care.\textsuperscript{51, 111} Though transport to definitive care at a tertiary care center should be conducted as soon as feasible, ALS has indeed been shown to improve outcomes in post-resuscitative care.\textsuperscript{33, 51, 52}

Induction of TTM in the prehospital setting appears to be of limited value.\textsuperscript{125, 129} Most studies have failed to show any improvement in survival for prehospital initiation of TH despite significant decreases in core temperature prior to arrival at the hospital.\textsuperscript{129} The increased risk of complications is possibly to blame suggesting TTM should not be initiated routinely in the prehospital setting.\textsuperscript{33, 34, 127} For OHCA where transport to a cardiac arrest center would take a significant period of time, it is possible that prehospital TTM could be of benefit, though no clear timeline was apparent from the literature.\textsuperscript{125}
The last component of Post-resuscitative care necessary is prevention of subsequent arrest. In the OOH setting, preventing arrest can be exceedingly difficult. Lack of detailed blood work, as well as limited equipment and medication resources, inhibits the ability to assess significant dysfunctions in electrolytes and other lab values. Furthermore, cardiac arrest is often the result of coronary artery occlusion and subsequent MI.\textsuperscript{57, 119} In the majority of these cases, coronary revascularization is necessary to decrease ischemia and to prevent recurrence of VF and subsequent arrest.\textsuperscript{1, 33, 51, 120} Because of these significant difficulties in preventing subsequent cardiac arrest, it should be considered good practice to transport OHCA patients to a dedicated post-resuscitation center.\textsuperscript{52, 120, 126}

\textit{Conclusion}

In the chaotic world of EMS, it can be difficult to adequately document acute patient interactions. Furthermore, it is not uncommon for responders to leave a call with only an approximate age and a hospital medical record number because the patient remains unidentified. Large studies can use statistical models for imputation and for interpolation based off of typical distribution of factors but this is imperfect.\textsuperscript{12} Furthermore, regional and interdepartmental differences in reporting can account for some variability if, for example, overdoses of opioid agonists are classified as cardiac arrest in one region but not another. Because of the inexact nature of emergency medicine, there will always be variation in results and in data reporting. The first step in advancing OHCA research is learning about what we do well and about what we can improve. To accomplish this, it is necessary to work towards a national database with
information on OHCA from the entire US so that not only can good, quality data be
collected, but also so that it can be distributed widely.\textsuperscript{1, 7, 14, 132} This improved
comprehension of the data we have on current performance can then be used to form a
unified approach to OHCA. It is our hope that some of the dramatic variation in OHCA
survival between regions can be addressed based on the suggestions contained herein.

More widespread training of the public in CPR is the second area which can and
should be utilized to improve survival from OHCA. In 1769, the city of Hamburg,
Germany passed an ordinance requiring notices to be read in church outlining the types of
assistance that should be rendered for persons who had drowned, frozen, been strangled
or otherwise incapacitated.\textsuperscript{1} While church is no longer a fundamental pillar of everyday
life as it once was, television PSAs have been shown to increase bystander CPR rate even
without self-reported increases in confidence and/or knowledge of CPR.\textsuperscript{70} CPR training
via self-teaching kits and open-access web formats have also been shown to increase
CPR certification and bystander CPR.\textsuperscript{68, 69} Including CPR training in schools and making
it a graduation requirement is a potential option to drastically improve training in CPR in
a relatively short period of time.\textsuperscript{7} In order to improve survival from OHCA, it is essential
that witnesses of SCA have the tools and training to make a difference.\textsuperscript{15, 16, 20, 21, 55-57, 64}
Improving access to, and familiarity with, AEDs can also make a substantial difference in
OHCA. Bystander use of AEDs is associated with a tremendous improvement in
survival.\textsuperscript{24, 25} The implementation and publicization of PAD is another potentially high
yield approach.\textsuperscript{7, 24-27} Improved DaCPR systems, which follow a uniform standard, have
been shown to improve survival outcomes as well.\textsuperscript{13, 20, 21, 57, 58} The combination of
improved bystander training, (in conjunction with GPS and mobile notification of local arrests) and PAD could be incorporated nicely into a strong DaCPR system. The ability to notify bystanders of a local AED is critical to early defibrillation.\textsuperscript{74}

Improved training of professional first responders is also critical to improved survival from OHCA. High quality CPR, of proper depth, rate, and recoil (See Appendix A - Table 4) is essential to good OHCA survival.\textsuperscript{72, 75} Training that involves the use of high fidelity simulation of OHCA, with real-time feedback and aggressive critique, is important to training rescuers to perform their best during real OHCA.\textsuperscript{1} The use of ALS interventions is of limited utility intra-arrest, and while important, post-resuscitative care is meaningless without ROSC from successful defibrillation.\textsuperscript{23, 28, 29, 105, 113} In general, an emphasis on high quality CPR and rapid deployment of AED by first responders will ultimately make the greatest difference in improving survival from OHCA.\textsuperscript{6, 7, 22, 23, 24, 25, 74,}
APPENDIX A – TABLES

Table 1: Incidence and Outcome of OHCA by Region

<table>
<thead>
<tr>
<th>Site Identity</th>
<th>Alabama N=267</th>
<th>Dallas N=1,265</th>
<th>Iowa N=565</th>
<th>Milwaukee N=801</th>
<th>Ottawa N=1,836</th>
<th>Pittsburgh N=575</th>
<th>Portland N=793</th>
<th>Seattle N=1,170</th>
<th>Toronto N=2,992</th>
<th>Vancouver N=1,634</th>
<th>Overall N=11,898</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Incid. Rate, per 100,000</td>
<td>40.3</td>
<td>82.9</td>
<td>51.3</td>
<td>86.7</td>
<td>45.1</td>
<td>51.1</td>
<td>47.0</td>
<td>74.4</td>
<td>57.0</td>
<td>52.8</td>
<td>56.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted Mort. Rate, per 100,000</td>
<td>36.9</td>
<td>77.2</td>
<td>44.4</td>
<td>78.0</td>
<td>42.3</td>
<td>47.1</td>
<td>41.0</td>
<td>62.3</td>
<td>53.6</td>
<td>46.9</td>
<td>50.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Case Fatality Rate, %</td>
<td>91.7</td>
<td>93.2</td>
<td>86.5</td>
<td>90.0</td>
<td>93.6</td>
<td>92.2</td>
<td>87.3</td>
<td>83.6</td>
<td>94.1</td>
<td>88.8</td>
<td>90.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival to Disch., %</td>
<td>3.0</td>
<td>4.2</td>
<td>11.3</td>
<td>9.9</td>
<td>5.3</td>
<td>7.1</td>
<td>10.4</td>
<td>16.2</td>
<td>5.2</td>
<td>9.8</td>
<td>7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vital Status Missing, %</td>
<td>5.3</td>
<td>2.7</td>
<td>2.3</td>
<td>0.1</td>
<td>1.1</td>
<td>0.7</td>
<td>2.3</td>
<td>0.2</td>
<td>0.7</td>
<td>1.4</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table shows data from Nichol et al.’s ROC. These data show incidence, mortality, survival, and incidence of missing data for all reported OHCA broken down by reporting region.
Table 2: Incidence and Outcome of VF OHCA by Region

<table>
<thead>
<tr>
<th>Site Identity</th>
<th>Alabama N=65</th>
<th>Dallas N=195</th>
<th>Iowa N=135</th>
<th>Milwaukee N=165</th>
<th>Ottawa N=429</th>
<th>Pittsburgh N=102</th>
<th>Portland N=249</th>
<th>Seattle N=297</th>
<th>Toronto N=614</th>
<th>Vancouver N=478</th>
<th>Overall N=2,729</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Incid. Rate, per 100,000</td>
<td>9.9</td>
<td>12.8</td>
<td>12.4</td>
<td>18.7</td>
<td>10.4</td>
<td>9.3</td>
<td>15.1</td>
<td>19.0</td>
<td>11.4</td>
<td>15.2</td>
<td>12.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted Mort. Rate, per 100,000</td>
<td>8.8</td>
<td>10.7</td>
<td>8.9</td>
<td>13.7</td>
<td>8.6</td>
<td>7.2</td>
<td>11.3</td>
<td>11.5</td>
<td>9.5</td>
<td>10.9</td>
<td>9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted Case Fatality Rate, %</td>
<td>89.2</td>
<td>83.3</td>
<td>71.9</td>
<td>73.4</td>
<td>83.5</td>
<td>77.0</td>
<td>75.2</td>
<td>60.2</td>
<td>83.5</td>
<td>71.8</td>
<td>76.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival to Disch., %</td>
<td>7.7</td>
<td>8.9</td>
<td>23.6</td>
<td>26.6</td>
<td>14.7</td>
<td>21.8</td>
<td>21.7</td>
<td>39.4</td>
<td>15.2</td>
<td>25.6</td>
<td>21.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vital Status Missing, %</td>
<td>3.1</td>
<td>7.7</td>
<td>4.5</td>
<td>0.0</td>
<td>1.9</td>
<td>1.1</td>
<td>3.1</td>
<td>0.4</td>
<td>1.4</td>
<td>2.6</td>
<td>2.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table shows data from Nichol et al.’s ROC. These data show incidence, mortality, survival, and incidence of missing data for OHCA with a first encountered rhythm of VF broken down by reporting regions.
Table 3: Three Phase Model of Cardiac Arrest

<table>
<thead>
<tr>
<th>Phase</th>
<th>Timing (approximate)</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical</td>
<td>first 4 minutes</td>
<td>-Early defibrillation can convert with high probability</td>
</tr>
<tr>
<td>Circulatory</td>
<td>4-10 min.</td>
<td>-Model suggests delayed defibrillation until after chest compressions to allow for tissue perfusion</td>
</tr>
<tr>
<td>Metabolic</td>
<td>after 10 minutes</td>
<td>-Tissue injury from global ischemia, resuscitation in this phase is significantly less likely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-leads to end organ damage and neurological deficit even with ROSC(^{38})</td>
</tr>
</tbody>
</table>

The table breaks down Weisfeldt’s “Three Phase Model of Cardiac” listing both the timing of the phases and the characteristics ascribed to each.\(^6\)
### TABLE 4: Critical Aspects of High Quality CPR
(Amended from Kleinman, 2015\textsuperscript{72})

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand Placement</td>
<td>Hand placement on lower half of the sternum</td>
</tr>
<tr>
<td>Compression Rate</td>
<td>100/min to 120/min</td>
</tr>
<tr>
<td>Compression Depth</td>
<td>At least 5 cm (2&quot;) but no more than 6 cm (2.4&quot;)</td>
</tr>
<tr>
<td>Chest Wall Recoil</td>
<td>Chest should be allowed to recoil without leaning on the chest</td>
</tr>
<tr>
<td>Compression Interruptions</td>
<td>Should be minimized as much as possible</td>
</tr>
<tr>
<td>Interruption for breaths</td>
<td>Should be less than 10s</td>
</tr>
<tr>
<td>Compression: Breath Ratio</td>
<td>30 compressions to 2 breaths without an advanced airway</td>
</tr>
</tbody>
</table>

Table shows current AHA recommendations for high quality CPR. Components include Hand Placement, Compression Rate and Depth, Chest Wall Recoil, Permissible Interruptions in Compressions, and the Ratio of Compressions to Breaths.\textsuperscript{72}
TABLE 5: RAPID DEFIBRILLATION V. ALS INTERVENTIONS  
(Amended from Stiell, 2004)\textsuperscript{113}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rapid Defibrillation</th>
<th>ALS</th>
<th>Percentage Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROSC</td>
<td>12.9</td>
<td>18</td>
<td>5.1</td>
</tr>
<tr>
<td>Admission</td>
<td>10.9</td>
<td>14.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>5</td>
<td>5.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Survivors with good CPC</td>
<td>78.3</td>
<td>66.8</td>
<td>-11.5</td>
</tr>
</tbody>
</table>

Table shows data reported by Stiell et al. demonstrating the percentage increase for ROSC, Survival to admission, Survival to discharge and Survivor Cerebral Performance Category\textsuperscript{*} (CPC) of 1 for patients treated with rapid defibrillation and ALS respectively. The data demonstrates their conclusion that rapid defibrillation, as opposed to ALS, is preferable for achieving survival with good neurological outcome.\textsuperscript{3,113}  
\textsuperscript{*}Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.\textsuperscript{114}
APPENDIX B- FIGURES

Figure 1: The Updated Chain of Survival (Adapted from Institute of Medicine Report).\(^7\) This figure depicts the chain of survival updated in 2010 by Rea et al. The chain represents the essential steps required to complete a successful resuscitation of SCA. Analysis of the resuscitation process by use of the chain of survival is a growing practice.\(^1,7,17,18\) [NOTE: spelling error in “Resuscitative” published in Federal report from which figure was taken]
Figure 2: 2015 Updated Utstein Template. Updated Utstein template for the reporting of cardiac arrest data. This simplified table provides a straightforward mechanism by which reliable data can be obtained across disparate agencies (Amended from Perkins, 2015).
Figure 3: Progression of VF Arrest. These three ECGs represent the progression of VF arrest from initial (highly defibrillatable) Coarse VF, to later (poorly defibrillatable) fine VF, to eventual Asystole (undefibrillatable). 

1. Asystole
Figure 4: Graphic Demonstration of Myocardial Stunning. Critical measures of cardiac function are displayed at Baseline (BL), 2 hours Post-ROSC (PR2), 4 hours Post-ROSC, and 72 hours Post-ROSC. The data shows significant, transient reduction in Stroke Volume (SV), Cardiac Output (CO), and Ejection Fraction (EF) corresponding to the period of described “myocardial stunning.”
Figure 5: Sequence for DaCPR. The figure demonstrates the sequence of instructions to be given to 911 callers in the case of suspected cardiac arrest. The extreme simplicity is designed to, ideally, reduce panic and improve likelihood of bystander intervention.\textsuperscript{57}
Figure 6: 2015 ACLS Cardiac Arrest Algorithm. Algorithm for the treatment of cardiac arrest by ALS personnel; presented in the 2016 AHA Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. This algorithm outlines the sequence of care for any ALS provider, including Paramedics, Nurses and Physicians.
Figure 7: Catecholamine Receptors Mechanism. β receptors and Dopamine 1 (DA-1) receptors activate adenylyl cyclase via Gαs, α2 and Dopamine 2 (DA-2) receptors interact with Gι which inhibits adenylyl cyclase. α1 receptors interact with Gq which activates PLC which triggers release of IP3, which releases Ca2+, and DAG, which activates PKC.102
### LIST OF JOURNAL ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acad Emerg Med</td>
<td>Academic Emergency Medicine</td>
</tr>
<tr>
<td>Am J Pharm Educ</td>
<td>American Journal of Pharmaceutical Education</td>
</tr>
<tr>
<td>Ann N Y Acad Sci</td>
<td>Annals of the New York Academy of Sciences</td>
</tr>
<tr>
<td>BMJ</td>
<td>BMJ: British Medical Journal</td>
</tr>
<tr>
<td>Crit Care</td>
<td>Critical Care</td>
</tr>
<tr>
<td>Circ Cardiovasc Qual Outc</td>
<td>Circulation: Cardiovascular Quality and Outcomes</td>
</tr>
<tr>
<td>Curr Opin Crit Care</td>
<td>Current Opinion in Critical Care</td>
</tr>
<tr>
<td>Curr Prob Cardiol</td>
<td>Current Problems in Cardiology</td>
</tr>
<tr>
<td>Emerg Medicine Journal</td>
<td>Emergency Medicine Journal</td>
</tr>
<tr>
<td>HSR Proc Intensive Care</td>
<td>HSR Proceedings in Intensive Care &amp; Cardiovascular</td>
</tr>
<tr>
<td>Cardiovascular Anesthesia</td>
<td>Anesthesia</td>
</tr>
<tr>
<td>Int J Nurs Educ Scholarsh</td>
<td>International Journal of Nursing Education Scholarship</td>
</tr>
<tr>
<td>J Am Coll Card</td>
<td>Journal of the American College of Cardiology</td>
</tr>
<tr>
<td>J Intern Med</td>
<td>Journal of Internal Medicine</td>
</tr>
<tr>
<td>J Thorac Dis</td>
<td>Journal of Thoracic Disease</td>
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VITA

NICHOLAS C. COCHRAN-CAGGIANO
14 Norfolk Rd. Chestnut Hill, MA
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1992

Education

Boston University, Boston, MA
MS in Medical Sciences, May 2016 anticipated graduation

Boston College, Chestnut Hill, MA
BA with a major in Theology, minor in history, May 2014

Phillips Exeter Academy, Exeter, NH
Secondary School Education, May 2010

Professional Experience

Lawrence General Hospital, Lawrence, MA- Trauma Technician
Conduct Electrocardiograms, Splint fractures, work under direction of Emergency Center Physicians and RNs.
   December 2015- Present

Cataldo Ambulance Service, Somerville, MA- Emergency Medical Technician, Field Training Officer
   Work as EMT-B in the Greater Boston area, Fenway Park and The TD Garden
   Instructor in CPR for local First Responders and company employees
   Train new EMTs to work in the field, assessing personality, knowledge and skills
   May 2014-Present

Lowell General Hospital. Lowell, MA-Emergency Room Technician
Conduct Electrocardiograms, Draw blood labs and cultures, splint fractures, work under direction of Emergency Department Physicians and RNs.
   June 2012- August 2014

PrideSTAR EMS, Lowell, MA- Emergency Medical Technician
   Work as EMT-B in Lawrence, Lowell, and Nashua; Practical Skills Teaching Assistant; Paramedic assistant in Emergent and Transfer situations
   April 2012- February 2016
Boston College EMS, Chestnut Hill, MA - Supervisor - Emergency Medical Technician Supervisor
Supervise and assist in training of new EMTs; EMT/Driver for BCEMS
Response vehicle, Member of Disaster Response Team; EMT for on campus events
August 2010 - May 2014

Boston College Department of Biology and Physics, Chestnut Hill, MA -
Undergraduate Research and Interdepartmental Fellow
Assist in design and construction of experimental laboratory equipment; apply principles and designed equipment to the analysis of Amyloid-β plaque aggregations
Assess fundamental components of myelin structure and function as well as dissection and sample preparation of nervous tissue for examination using X-ray Diffraction.
January 2011 - May 2013

Skills and Certifications
- EMT-B MA, NH, NREMT (since 04/2011)
- CPR (since 2008), BLS Instructor (since 11/2015)
- Advanced Cardiac Life Support (since 06/2013)
- Pre-Hospital Trauma Life Support (since 08/2014)
- International Trauma Life Support (since 08/2015)
- Chemical Hygiene Training (OSHA 29 CFR 1910.1450)
- Biohazard Waste Management Training (EPA 40CFR262.40)
- Radiation Safety Training (NRC 10 CFR 20)
- Hazardous Materials Awareness, Operations Training
- NIMS 100, 200, 700, 701, 800
- Computer Skills: MS Word, MS Excel, Adobe InDesign
- Languages: English (Native), Spanish (Speak, Read, Write)