REFRACTORY CARDIAC ARREST: NEW TECHNIQUES AND SOLUTIONS TO AN OLD PROBLEM

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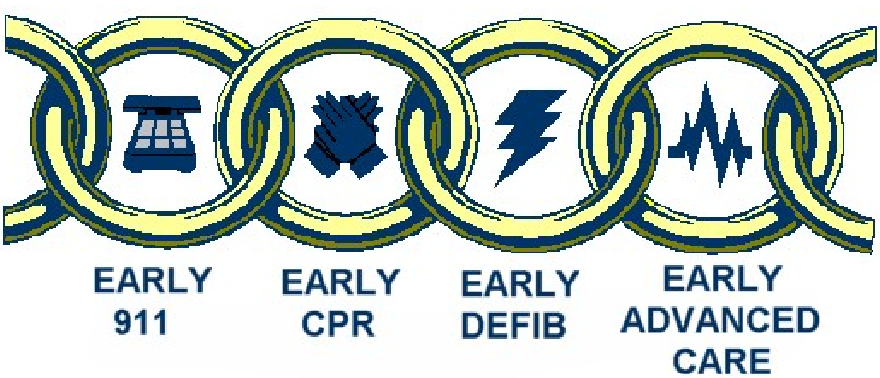
INTRODUCTION

Approximately 95% of all patients who suffer from sudden cardiac death (SCD) die before reaching the hospital.[1] It is estimated that 875,000 Americans suffer from cardiovascular disease and of those, 50% will have cardiac arrest as their first manifestation of coronary artery disease. [1,2] SCD accounts for over 325,000 annual out-of-hospital deaths. [1] Brain death during cardiac arrest starts after only four to six minutes without any intervention. As a result, cardiopulmonary resuscitation (CPR) and advanced cardiac life support (ACLS) training were developed in attempt to improve both out-of-hospital and in-hospital cardiac deaths.

CPR and ACLS are a series of emergency procedures that were originally developed to circulate and oxygenate blood, as well as return the body to spontaneous circulation. CPR is designed to provide basic circulation and oxygenation. ACLS is a higher level of specialized training that involves arrhythmia recognition, electrical defibrillation, airway management, and the use of intravenous (IV) medications that can improve the victim's chance of return to spontaneous circulation (ROSC). CPR and ACLS are important steps in the "chain of survival" which include 1) recognition of early warning signs, 2) activation of emergency medical system, 3) basic CPR, 4) defibrillation, 5) intubation, and 6) IV administration of medications (figure 1). [6] Unfortunately, despite training over 7 million Americans annually in the practice of CPR, sudden cardiac death occurring out-of-hospital carries a survival rate of approximately 6%. [1,3] In addition, despite rapid recognition and the presence of highly trained personnel, in-hospital cardiac arrest has an equally poor survival rate at 5-15% with even worse outcomes should resuscitation efforts continue for over 30 minutes, an area since termed refractory cardiac arrest. [4] To date, there are no widely available treatment options for prolonged or refractory cardiac arrest. However, recent research has demonstrated that in-hospital and out-of-hospital survival from cardiac arrest can be potentially improved by implementing a variety of simple and advanced measures.

Figure 1



HISTORY OF CPR

It is believed that the first resuscitation effort was described in the bible at around 800 BC. Kings chapter 4 of the bible describes the prophet Elisha's attempt to resuscitate a child when he "went up, and lay upon the child, and put his mouth upon his mouth, and his eyes upon his eyes, and his hands upon his hands; and he stretched himself upon the child; and the flesh of the child waxed warm." [7] Shortly thereafter, it was discovered that heat was connected to life and that the body became cold when lifeless. As a result, attempts were made to restore life by placing warms ashes, hot water, or burning excrement on the body and, even later in time, by whipping the victim to stimulate a response. [7] It was not until the 1530s with the development of the Bellows method, whereby hot air and smoke from a fireplace were blown into a victim's mouth, that any of the current resuscitation practices were derived. This method was further advanced approximately 200 years later with Fumigation method in which Native Americans would blow tobacco into an animal bladder and then into the victim's rectum. However, the English did not adopt this practice for long since research in the mid 18th century demonstrated that even small amounts of tobacco could kill cats and dogs.[7]

For the next several decades, different techniques including inverting victims from their feet (figure 2), bloodletting, and tactile stimulation were used in attempt to restore life to those that had died. In the late 18th century and early 19th century it was finally discovered that air should be rhythmically moved into and out of the chest for better success. Subsequently, victims were rolled over barrels and placed on the back of a trotting horse in attempts to alternate compression and relaxation of the chest cavity. [7] Surprisingly, it was not until World War II that mouth-to-mouth resuscitation was adopted and practiced by the United States military. During the 1950s, the American Red Cross began educating the public on the role of mouth-to-mouth resuscitation in cardiac death. [7] Recommendations for formal cardiac massage came shortly thereafter in the 1960's when Dr. Kowenhoven described the crucial aspect of the patient receiving oxygen to the brain by the development of minimal blood circulation.[7] It was based on these recommendations that the formal CPR known today was derived.

Figure 2

THE OUT-OF-HOSPITAL ARREST

Despite the drastic improvement in emergency care services and access to prompt medical attention, mortality amongst patients who suffer a cardiac arrest out of a hospital continues to be approximately 85-97%. [8] Numerous studies have been conducted on all aspects of the chain of survival in attempt to increase survival to hospital admission and eventual hospital discharge. The importance of initiation and quality basic CPR has become increasingly important in the ultimate survival from SCD. Several studies have documented the importance and improved outcomes that result from quality CPR. [12, 13] When originally instructed on mannequins, first responders including EMTs, paramedics, police offices and firefighters, are evaluated on their ability to provide correct speed and depth of chest compressions as well as minimize CPR-free intervals. It has been shown repeatedly that quality of chest compressions only several months after original instruction deteriorate significantly when retested again on mannequins. [10,11] Subsequently, it was inferred that true life arrest scenarios would also suffer the same deterioration leading to a decrease in survival as compared to optimal CPR.

Wik et al in 2005 set out to determine whether the guidelines by the American Heart Association (AHA) for compressions, ventilations, and CPR free intervals were adhered to during advanced cardiac life support in the field. To complete this task, defibrillators were fitted with extra chest pads to be mounted on the lower part of the sternum and fitted with accelerometers. [9] Eighteen ambulances, staffed by paramedics and some nurse anesthetists in varying countries throughout Europe, were equipped with these specialized defibrillators and 176 adult patients with cardiac arrest were monitored over 1.5 years. The results showed that chest compressions were not given 48% of the time that there was no spontaneous circulation (table 1). Even after correction for time associated with defibrillation and rhythm analysis, no-flow was observed during 38% of the time, significantly higher than the AHA recommendations of <20%. [9] Frequency of compressions, recommended by the AHA to be 100 compressions per minute (cpm), was recorded at an average of 60 cpm during the first five minutes of cardiac arrest and 64 cpm when averaged over the entire episode of CPR. Depth of compressions was also only satisfactory with approx 1 of 4 compressions being the correct depth of 38-51mm. Fortunately, in comparison to other previously published studies, there were no abnormally high ventilation rates. Regrettably, there was no analysis to correlate these results to survival data and, therefore, it can only be speculated, based on previous studies, that survival outcome would decrease as a result of substandard CPR.

Table 1

. Performance of CPR During the First 5 Minutes and Entire Episode of CPR*

	First 5 Minutes of CPR	Entire Episode of CPR
No flow (n = 176)		
NFR, %	49 (21)	48 (18)
NFR_{adj}, %	42 (19)	38 (17)
Compression (n = 176)†		
Compressions/min	60 (25)	64 (23)
Compression rate, /min	120 (20)	121 (18)
Depth per episode, mm	35 (10)	34 (9)
38-51 mm with complete release	27 (30)	28 (25)
Too deep (>51 mm), median (IQR)	0 (0-3)	0 (0-5)
Too shallow (<38 mm)	59 (37)	62 (33)
Incomplete release, median (IQR), %	0 (0-1)	0 (0-2)
Duty cycle, %	41 (5)	42 (4)
Ventilation (n = 163)		
Ventilations/min	8 (4.6)	11 (4.7)

Abbreviations: CPR, cardiopulmonary resuscitation; IQR, interquartile range; NFR, no-flow ratio, the time without CPR as a percentage of the time without spontaneous circulation; NFR_{adj}, no-flow ratio, adjusted by subtracting time allowed for electrocardiographic analysis, possible defibrillation, and required pulse checks in the numerator.

*All data are expressed as mean (SD) unless otherwise noted.

†Compressions per minute refer to the actual number of compressions delivered per minute whereas compression rate refers to the mean rate of compressions, ie, the reciprocal of intervals between compressions in compression sequences.

In addition to quality of CPR, response time to initiation of bystander CPR, basic and advanced cardiac life support, and transport time to nearest hospital are important factors in the survival of prehospital cardiac arrest. In 2005, Vukmir published a prospective multi-center trial evaluating the correlation between survival from out-of-hospital cardiac arrest and the timing/initiation of varying forms of basic life support. Eight hundred and seventy four adult patients who suffered out-of-hospital cardiac arrest within 30 minutes of the nearest hospital were evaluated based arrest times and subsequent intervention times to initiation of bystander CPR, basic life support, advanced care life support, ROSC, and scene to hospital transit time. [14] The primary patient outcomes were time to ROSC measured by palpable pulses and also initial emergency department survival. Survival was improved with decreased time to initiation of bystander CPR, basic life support, and advance cardiac life support (table 2). Cumulative survival rate at 13.9% was consistent with numerous other reports of average survival from out-of-hospital arrest. Additionally, no patient in this study survived if interval to initiation of ACLS exceeded 30 minutes or if time to hospital emergency department was beyond 90 minutes. Interestingly, time to ROSC was longer in survivors in comparison to non-survivors at 27.27 min versus 20.73 min respectively (p=0.006). [14] This may suggest that those who fail initial defibrillation may need additional time of basic life support before stunned myocardium can increase cardiac output enough to create a palpable pulse and perfusion pressure. This theory has been shown to carry some merit in animal models where cardiac output was monitored immediately following defibrillation and it likely played an important role in the 2006 AHA update on ACLS recommendations for continued chest compressions two minutes after defibrillation before analysis of rhythm and palpation of pulse. Regardless, it is obvious that rapid response by even lay rescuers plays an important role in the chain to survival.

Table 2

Response time correlation to ER survival

	Time interval				*t*-Test (*p*)
	Mean (min)	Range (min)	Survivors (min)	Non-survivors (min)	
ByCPR *N* = 259	2.08 ± 2.77	0–21	1.58 ± 1.71 39	2.20 ± 2.79 189	0.07
BLS *N* = 484	6.63 ± 5.73	0–35	5.52 ± 4.75 570	6.81 ± 5.66 361	0.047
ACLS *N* = 618	9.08 ± 6.31	0–40	7.29 ± 5.76 88	9.49 ± 6.30 475	0.002
ROSC *N* = 148	4.96 ± 13.55	0–98	27.27 ± 13.71 77	20.73 ± 12.82 56	0.006
Hospital *N* = 533	41.05 ± 11.68	0–92	39.69 ± 12.91 78	41.65 ± 11.31 402	0.214

In response to numerous studies showing that timely advanced care life support improved outcomes in out-of-hospital cardiac arrest, investigation was focused on how to improve times to definitive intervention, namely rapid defibrillation. Ventricular fibrillation is the most commonly encountered initial rhythm during cardiac arrest accounting for over 50% of all arrests. Previously, trials had focused on increasing emergency personnel who are trained to provide defibrillation as well as decreasing response times of emergency medical services. Given the difficult to manage constraints on response time such as varying degrees of traffic, high rise buildings, and rural locations of cardiac arrest, investigation was pursued into providing public access to portable defibrillators in prime locations for cardiac arrest in attempt to provide bystander or lay rescuers opportunity to decrease time to initial defibrillation. Early case reports of successful deployment of automated external defibrillators (AEDs) in casinos and airports prompted a large, governmental funded trial to investigate the feasibility, cost, and efficacy of large-scale placement of AEDs in public areas. [8]

The PAD (public access defibrillation) trial was published in 2004 by the New England Journal of Medicine and involved 24 participating research sites enrolling 993 community units including shopping malls, airports, high-rise residential buildings and business parks. Volunteers in these areas were trained in the use of the AEDs and trained to recognize cardiac arrest. Two-hundred and thirty seven arrests were randomized to either intervention with AED and basic CPR or CPR only. Survival was doubled in the intervention group with 30 survivors among 130 arrests versus 15 survivors among 107 arrests in the CPR only group (p=0.03, relative risk = 2.0, 95% CI 1.07-3.77). [8, 15] However, survival was not improved across all venues for AEDs. Out-of-hospital cardiac arrest in residential facilities was poor in both groups with only 1 survivor in each group among 70 arrests. Cost analysis for each additional life saved was found to be incremental based on the frequency of arrests and survival rates (table 3) with the greatest cost-effectiveness of placing AEDs in facilities were cardiac arrests are relatively frequent with at least 1 every 2-years. [8]

Table 3

TABLE
*Hypothetical Incremental Program Cost-Effectiveness of PAD**

Number of cardiac arrests occurring at facility	Survival rate with AED + CPR†		
	10%	20%	30%
1 per 10 years	$430,000	$215,000	$143,333
1 per 5 years	$215,000	$107,000	$ 71,667
1 per year	$ 43,000	$ 21,500	$ 14,333
2 per year	$ 21,500	$ 10,750	$ 7,167

*Cost of each additional life saved computed as:

$$\frac{\text{(average yearly AED+CPR cost – average yearly CPR-only cost)}}{\text{(expected \#AED+CPR survivors/yr – expected \#CPR-only survivors/yr)}}$$

†Assumes survival is doubled with a community-based CPR+AED program, compared to a CPR-only program.

Historically epinephrine has been the first line agent for treatment of cardiac arrest. [8] However, recent literature has put in question whether vasopressin, a naturally occurring antidiuretic hormone which at high doses acts as a vasoconstrictor, would be superior to epinephrine in refractory out-of-hospital cardiac arrest. Credence for this theory came from Linder et al observations in 1990s of higher endogenous vasopressin concentrations among survivors of cardiac arrest in comparison to those without any ROSC. [16] Further subsequent studies also showed that during a cardiac arrest vasopressin will increase blood flow to vital organs, increase chance for survival, and improve neurological outcomes. [8]

In 2004, a 33-month long, large scale, double-blinded, multicenter trial was published in the New England Journal of Medicine on 1,186 patients who suffered out-of-hospital cardiac arrest. [17]. Adult patients who presented with ventricular fibrillation, asystole, or pulseless electrical activity (PEA) requiring CPR were randomized to either receive epinephrine or vasopressin (40 IU dose). The protocol allowed for injection of the study drug followed by 20ml of normal saline which was to be repeated in three minutes if there was no ROSC. After the second dose of the study drug, physicians were allowed to give additional doses of epinephrine or any other drug combination felt necessary. The results showed that for patients who originally presented in asystole, those who received vasopressin had statistically significant higher rates of hospital admission and subsequent hospital discharge at 29% and 4.7% respectively in comparison to the epinephrine group at 20.3% and 1.5%. Patients with ventricular fibrillation or PEA did not see any significant differences in treatment with vasopressin versus epinephrine. In addition, 732 patients with refractory PEA cardiac arrest having been treated originally with vasopressin and then subsequently with epinephrine were more likely to survive to hospital admission (25.7% vs 16.4% p=0.002) and to hospital discharge (6.2% vs 1.7% p=0.002) compared to those treated with epinephrine alone. The authors concluded that epinephrine was not superior to vasopressin in ventricular fibrillation and PEA arrests. In addition, the authors concluded that vasopressin is superior to epinephrine for out-of-hospital cardiac arrest due to asystole and the combination of vasopressin plus epinephrine is superior to epinephrine alone in refractory PEA cardiac arrest. Unfortunately, these results have not been widely reproducible with multiple other studies showing variable results with vasopressin. [18, 19] According to the 2005 update, vasopressin is still rated as "indeterminate" for PEA and should be "considered" during original asystolic arrest.

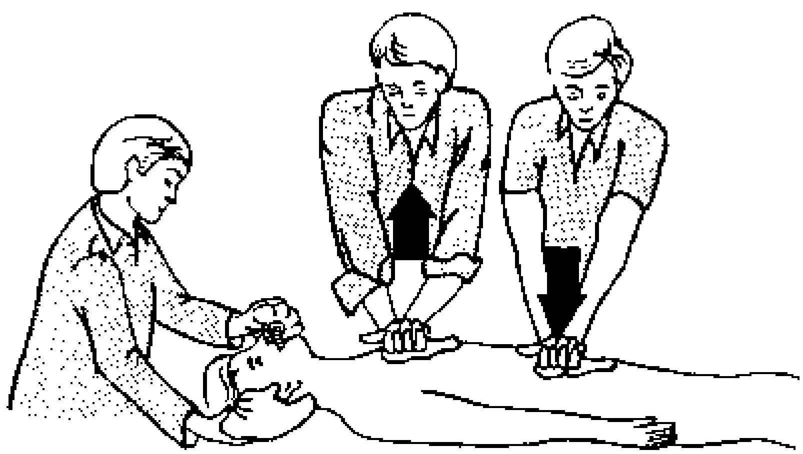
Although traditional CPR is important in the chain of survival, there have been numerous studies investigating alternative CPR techniques. As detailed previously, quality of chest compressions is important to overall survival from a cardiac arrest. In attempts to improve or standardize quality of chest compressions, there have been numerous experimental studies on developing mechanical CPR devices. Widely commercially available automatic piston-like devices, which are set to a given compression depth and rate, have failed to show improved hemodynamic variables and are, at best, similar to manual compression. [8] Other devices with similar mechanical backgrounds include active compression and decompression pistons which are used to actively push down and pull up on the patient's sternum. In an attempt to generate additional negative intrathoracic pressures, these devices are theoretically designed to improve venous return in their active decompression phase in comparison to standard CPR. Unfortunately, European trials of prehospital arrest have failed to show consistent data with any proven benefit and moreover, these devices have shown a higher incidence of rib fractures leaving them rarely used in the United States. [8]

Contrary to traditional CPR which involves both chest compressions and mouth-to-mouth resuscitation, a growing body of evidence shows no significant change in survival amongst patients receiving compression only CPR. [8] In 2000, Hallstrom et al published in the New England Journal of Medicine a randomized trial of 241 witness cardiac arrests where emergency phone operators randomized instructions given to bystanders for either compression only CPR or traditional mouth-to-mouth resuscitation. The authors found that instructions for compression only CPR given by phone operators to bystanders required 1.4 minutes less than instructions for traditional CPR (p =0.005). [20]

Additionally, there was no statistically significant benefit of survival to hospital discharge with traditional CPR over the compression only. Considering the reluctance of bystanders to perform mouth-to-mouth resuscitation and previous observational studies confirming the conclusion of Hallstrom et al, compression only CPR is faster and easier to instruct lay rescuers and may reduce the 50% of all witnessed arrests in which no bystander engaged in any form of CPR. [8, 20]

Additional alternative CPR techniques have been described in the literature to have improved survival to hospital discharge. Interposed abdominal compression cardiopulmonary resuscitation (IAC-CPR) involves compression of the abdomen in alternation with compression of the chest during resuscitation (figure 3). [8] It was first described in 1957 and used as an adjunct to CPR in 1981. Three randomized control trails have been conducted comparing IAC-CPR to standard CPR. The largest of these studies demonstrated significant improvement in ROSC (51% vs 27%) and survival to hospital discharge (25% vs 7%) with the use if IAC-CPR during in-hospital cardiac arrest in comparison to standard CPR. [8] Furthermore, no significant complications, including increased risk of emesis or aspiration, were noted in the study suggesting that use of IAC-CPR may be of benefit if instructed for in-hospital cardiac arrest. [21]

Figure 3



THE IN-HOSPITAL ARREST

Despite the presence and proximity of ACLS certified medical personnel and relatively short response time to initiation of CPR after witnessed arrest, in-hospital cardiac arrest, especially in the elderly, continues to have poor survival to hospital discharge. [22] Additionally, in patients younger than 75 years old, lengthy resuscitation efforts without further experimental rescue efforts often results in death. Accordingly, research has recently focused on use the extracorporeal membrane oxygenation (ECMO) as a means to adjunct CPR techniques, termed E-CPR, in cases of prolonged or refractory cardiac arrest.

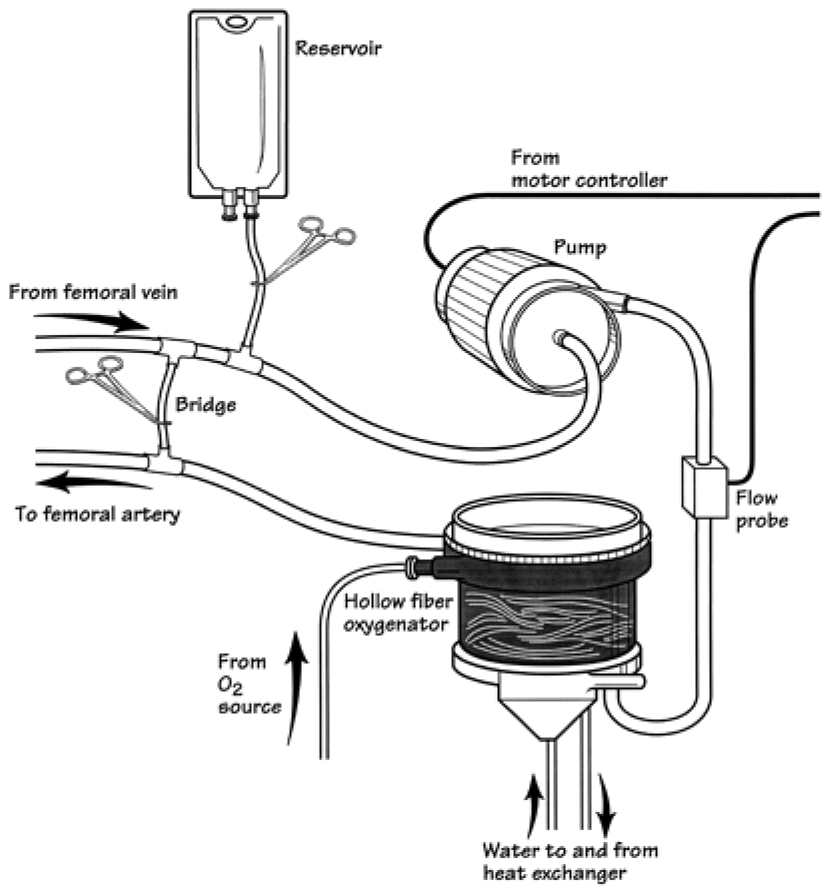
Extracorporeal life support has been well established as a means of support for perioperative cardiac patients and severe cardiomyopathies. [23] In 1992, the use of ECMO as rescue therapy to children with cardiac disease who failed conventional ACLS was published by del Nido et al [24] and demonstrated improved survival. Since this study, numerous investigation clinical trials have reproduced similar data in children showing consistently improved survival with the use of E-CPR in refractory cardiac arrest. [5, 25, 26] Furthermore, E-CPR has been shown to promote survival in cases of prolonged cardiac arrest in children of upwards of 95 minutes. [5] It was not until the mid-1990s that investigation in the use of E-CPR as a means of rescue in adults with refractory cardiac arrest began publishing.

ECMO is a technique to provide both cardiac circulation and blood oxygenation in cases of severely injured or diseased primary organs. The device is placed at bedside and is comprised of a continuous pump which circulates blood from the patient through a membrane oxygenator that imitates the gas exchange of the lungs and then returns oxygenated blood to the patient (figure 4). There are two main types of ECMO, veno-arterial (VA) and veno-venous (VV). In both, blood is drained from the venous system to be oxygenated outside of the body. However, in VA ECMO, the blood is returned to the arterial system versus the venous system in VV ECMO. VV ECMO results in no cardiac support and therefore is not used for E-CPR. To initiate E-CPR, cannulation must occur of both artey and vein with a 15- to 17-F cannual and 23- to 29-F cannual respecitvely. Exposure of the artery and vein are achived using a modified Seldinger technique. Most common sites for cannulation during cardiac arrests are femoral artery and vein, and carotid artery/jugular vein, however, superior venal cavus and aorta have also been described in patients immeadiatley post-cardiac surgery. Initiation of entire procedure generally takes between 15-45 mintues.

Success associated with E-CPR techniques varies from study to study. However, in general, most studies have found greater survival rates with the use of E-CPR in refractory cardiac arrest over standard CPR. More specifically, E-CPR is considered for patients who traditional CPR and ACLS logorhythms have failed to produce ROSC and death is imminent. Subsequently, any survival from this group of patients represents a positive outcome where traditional techniques would have almost guaranteed non-survival. Selection of patients that would potentially benefit from the use of E-CPR is heterogenous and differs from each clinical trial.

In 1999, Younger et al[4] published data on the use of E-CPR in 25 patients over a period of seven years. Patients in continuous cardiac arrest or immediately post-cardiac arrest were considered. Overall survival was reported at 36% (9 patients of 25). Survivors had a significantly shorter duration of CPR prior to E-CPR (21 minutes vs 43 minutes in non-survivors, $p= 0.04$). [4] Of the nine survivors, seven were discharged to home with minimal to no neurological compromise which did not prevent them from returning to work. The remaining two survivors were still awaiting heart transplant at the conclusion of the study. Six of the nine survivors had initial events pulmonary in nature (pulmonary embolus, air embolism, airway obstruction) while two others experienced acute myocardial infarctions while in a cardiac procedure lab. The authors concluded that patients in which an immediate "curable disease," such as pulmonary embolus or surgically amenable CAD, was present at time of arrest would benefit from E-CPR above those with advanced age or prolonged illness. In addition, patients who have witnessed arrest during evaluation or treatment also stand to benefit from E-CPR. [4]

Figure 4



A smaller experience with emergency E-CPR was described by Magovern et al [27] in which 6 patients over 6 years were placed on ECMO during cardiac arrest. In this retrospective analysis, indications for use of ECMO were mostly limited to patients in cardiogenic shock from postcardiotomies, high-risk cardiology interventions, and perioperative cardiac graft failure. All of the six patients who received E-CPR suffered a sudden cardiac collapse in the catherization laboratory or medical intensive care unit. Their average age was relatively young in comparison to other studies with E-CPR at 59.3 years ± 4.3 years. Unfortunately, none of these six patients were able to wean from ECMO with a mean length of assist at 43.2 hours, a result the authors attribute to complications of severe neurological insult in conjunction with cardiac collapse. Since no total arrest times nor prior neurological function of this small group of patients were noted in this analysis, it is difficult to draw conclusions as whether E-CPR would have been successful if implemented sooner during the arrest of these patients.

The two largest and most recent retrospective analyses of experience with E-CPR demonstrated similar survival rates to hospital discharge as Younger et al. [14, 28, 29] Chen et al [28] selected patients with a variety of resuscitation times from <30minutes to >60minutes in which they reported survivors at all time groups (table 4) with a total survival rate of 31.6% (18 out of 57). Only one patient of three who survived after prolonged CPR of >60minutes suffered severe neurological deficit. Similar to previous trials, survivors had a much shorter duration of CPR (39.2 ± 13.7 min in survivors vs 51.5 ± 11.3 min in non-survivors p=0.0014). [28] Once again, patient selection was integral to the success of E-CPR with 96.5% of arrest being witnessed and 100% survival with CPR duration of <30minutes.

Massetti et al [29] in 2005 speculated that quality of CPR was more important than duration of resuscitation efforts as they reported an overall survival rate of 20%, with 4 of their 8 survivors having CPR for between 90-120 minutes (table 5). However, their overall survival rate was lower than previously reported in other experiences and likely is contributed by the fact that none of their E-CPR attempts were conducted in patients with traditional CPR duration of <30minutes, a time frame most other reports found a high level of success within. The impact of definitive reversible treatment on survival has also been consistent in the literature. Reports of arrest from pulmonary/air embolism, acute myocardial infarction amenable to surgical intervention, and cardiotoxic drug intoxication have shown favorable outcomes with definitive treatment further supporting the need for careful patient selection in the use of E-CPR. [23, 28, 29, 38]

Table 4

Relationship Between Weaning or Survival and CPR Duration

CPR Duration	n	%	Weaning n (%)	Survival n (%)
<15 min	0	0		
<30 min	2	3.5	2 (100%)	2 (100%)
<45 min	14	24.56	11 (78.57%)	8 (57.14%)†
<60 min	31	54.39	25 (80.65%)*	15 (48.39%)*
>60 min	26	46.61	13 (50%)	3 (11.5%)
Total	57	100	38 (66.7%)	18 (31.6%)

CPR = cardiopulmonary resuscitation

Table 5

Relationship Between Outcome and Cardiopulmonary Resuscitation Duration

ECM Duration	All Population n = 40	Death < 24 H n = 22	Survival n = 8
< 30 mn	0	0	0
< 60 mn	8	0	3
< 90 mn	11	6	4
< 120 mn	7	6	0
> 120 mn	10	8	1
unknown	4	2	0
Mean time (mn)	105 ± 44	129 ± 34	79 ± 39[a]
Range (mn)	35 to 200	75 to 200	45 to 170

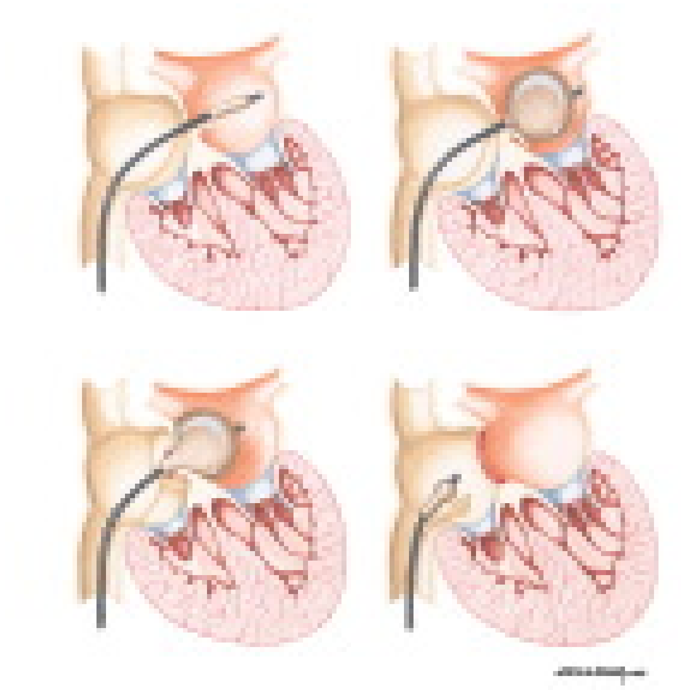
[a] = $p < 0.001$.

ECM = external cardicac massage; mn = minutes.

Although use of E-CPR in select patients appears favorable and promising, complications and feasibility of implementing E-CPR programs remain significant. Complications from E-CPR are almost universally reported to include need for surgical revision of the cannulation site, massive transfusions requirements, and limb ischemia. Limb ischemia, a result of arterial steal from the cannulated leg, can be successfully avoided by secondary cannulation of the distal limb. [23] Unique to the use of ECMO is the difficulty of stunned myocardium being able to generate enough pressure to open the aortic valve against the pressure generated by the ECMO circuit.[4] As a result, the left ventricle would slowly fill with blood from the pulmonary vein causing progressive over-distension of the ventricle and elevated transmural pressures with potential free wall rupture. This is monitored by ensuring that pulsatile arterial line waveforms are achieved. If there is no pulsatility, patients would need to undergo a left ventricle venting procedure by which percutaneous atrial balloon septostomy was performed (figure 5).

Feasibility of using E-CPR requires a multidisciplinary team approach. Given the technical nature of ECMO and emergency need for E-CPR, specialized flow engineers must be on-call 24-hours to facilitate setup for use. In addition, nursing staff must be trained in the emergency setup and continuous use of the machines. Senior cardiac surgeons and intensivists must be available for emergency cannulation, as well as cardiologists for possible emergency percutaneous cardiac intervention and multiple daily evaluations of left ventricular function by echocardiography. Cost-effectiveness has not been directly evaluated. However, it has been estimated to cost $2,800 for the disposable circuit to the device alone. This cost was speculated to be less expensive than alternative treatments such as immediate implantation of uni- or bi-VAD alternatives in refractory cardiac arrest.[29] Nevertheless, no cost-analysis for total implementation of an E-CPR program per life saved has been undertaken in the literature and may likely prove to be excessive in comparison to the number of candidates in which it will be able to promote survival. E-CPR does appear to be a promising technique in refractory cardiac arrest of select patients, however, future exploration of cost-analysis and consistent exclusion criteria must be agreed upon before conclusions as to its practical use are made.

Figure 5



Although use of E-CPR appears promising in restoring spontaneous cardiac circulation in refractory cardiac arrest, there are still a large number of patients with both in-hospital and out-of-hospital cardiac arrest who suffer from moderate to severe neurological injury resulting in either death or poor quality of life. In the US, permanent brain damage after CPR results in delayed deaths and can be seen in 10 to 30% of all survivors of out-of-hospital cardiac arrest.[30] In response to the unsatisfactory failures from traditional CPR and brain ischemia from prolonged resuscitation efforts, investigation into induced therapeutic hypothermia (TH) after cardiac arrest has gained interesting press in the medical community within the last 10 years. Hypothermia as a protective entity on the brain was first used for special surgical procedures in the 1950s. The concept of using TH for improving neurological outcomes after cardiac arrest was not postulated until the late 1980s when accidental hypothermia in animal models was shown to be protective.[30] Although originally thought to result form reduction in oxygen requirements, TH's benefits on neurological outcome appear to be multifactorial.[31, 32]

In 2002, the New England Journal of Medicine published two landmark randomized control trials of TH to improve neurological outcomes in patients after cardiac arrest from ventricular fibrillation. [31, 33] The first trial, an Australian evaluation of 77 patients who suffered out-of-hospital cardiac arrest with original rhythm being ventricular fibrillation, randomized patients who had successful ROSC to either TH with external cooling packs or standard resuscitation. Any patients who meet criteria for cardiogenic shock, defined as a systolic blood pressure of less than 90mmHg despite epinephrine infusion, were excluded from the trial. Those assigned to TH were induced to a core body temperature of 33ºC within 2 hrs after ROSC and maintained at that temperature for 12 hrs before return to normothermia by 48 hrs. [33] The results were very impressive with 21 of 43 patients treated with hypothermia (49 percent) surviving with a good outcome (i.e. discharged to home or rehabilitation facility) versus 9 of 34 patients in the control group (26 percent, p= 0.046).

Similarly, the European trial published in the same issue of New England Journal of Medicine randomized 275 patients to treatment with TH by means of an external cooling device, employing cool circulating air, to patients with witnessed cardiac arrest from pulseless ventricular tachycardia or ventricular fibrillation. [31] Patients with first attempt at CPR longer than 15 minutes from time of collapse or who had no identifiable ROSC within 60 minutes from time of collapse were excluded, as well as those with cardiogenic shock after ROSC. Patients in the TH group were maintained at 32 ºC to 34º C for 24 hours and then slowly warmed to normothermia by 48hrs. Once again, results were very favorable with 55% (75 of 136 patients) of TH group having a favorable neurological outcome as compared to 39% (54 of 137 patients, p=0.009) in the normothermia group (table 6, figure 6).

Table 6

Neurologic Outcome and Mortality at Six Months.

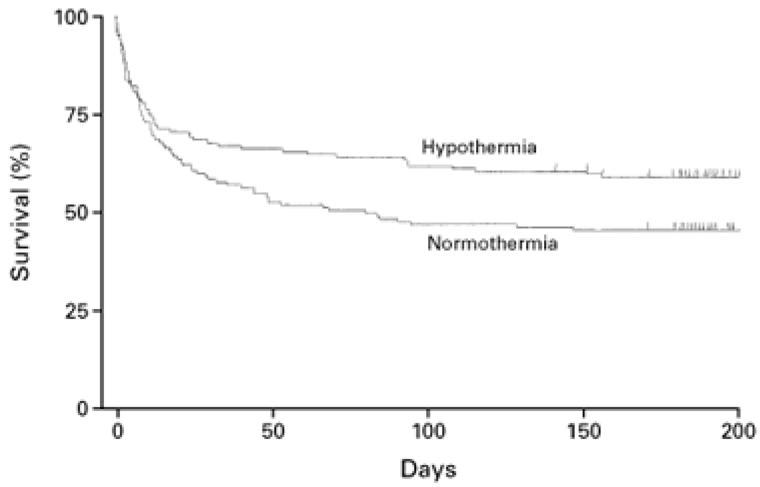
Outcome	Normothermia	Hypothermia	Risk Ratio (95% CI)*	P Value†
	no./total no. (%)			
Favorable neurologic outcome‡	54/137 (39)	75/136 (55)	1.40 (1.08–1.81)	0.009
Death	76/138 (55)	56/137 (41)	0.74 (0.58–0.95)	0.02

*The risk ratio was calculated as the rate of a favorable neurologic outcome or the rate of death in the hypothermia group divided by the rate in the normothermia group. CI denotes confidence interval.

†Two-sided P values are based on Pearson's chi-square tests.

‡A favorable neurologic outcome was defined as a cerebral-performance category of 1 (good recovery) or 2 (moderate disability). One patient in the normothermia group and one in the hypothermia group were lost to neurologic follow-up.

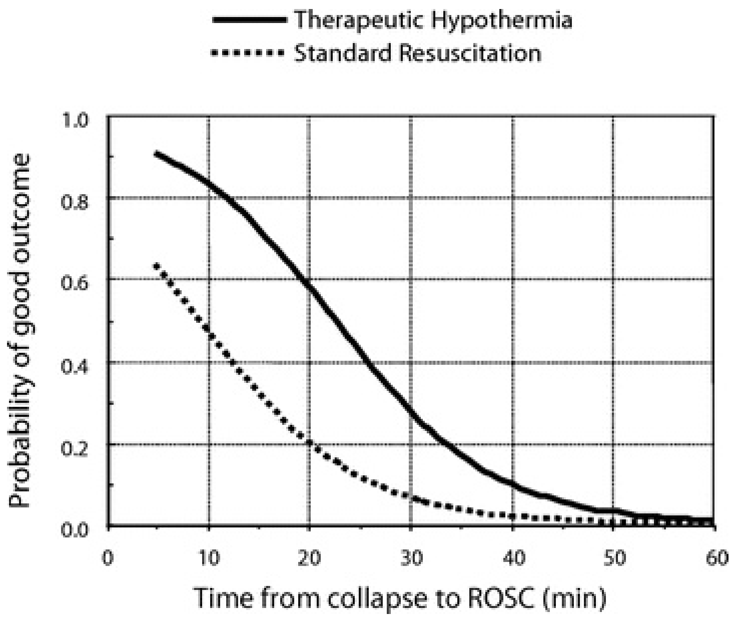
Figure 6



Although both studies showed very promising results with TH after cardiac arrest, their study population was limited to patients with original ventricular fibrillation or pulseless ventricular tachycardia arrests. In addition, all patients with cardiogenic shock were excluded making real world implementations questionable. Therefore, in 2006, Oddo et al [34] published a retrospective study of TH in ICU based patients who had out-of-hospital cardiac arrest with all ventricular and non-ventricular rhythms (pulseless electrical activity, asystole). In addition, this study included patients who met criteria for cardiogenic shock on inotropes. The authors found similar rates of favorable outcomes in comparison to previous studies. Specifically, patients treated with TH who suffered original ventricular fibrillation arrest had an overall survival rate with good neurological outcome at 55.8% compared to 25.6% in the standard resuscitation group (p=0.004). In addition, they found similar benefits of TH in patients with shock (good outcome in 5 of 17 patients in TH group versus zero of 14 patients in standard therapy, p=0.027), a finding that was not included in previous studies. Unfortunately, outcomes for patients with asystole or PEA were universally poor with only 3 total survivors out of 23 arrests regardless of treatment.

Although very favorable, these cumulative results continue to support the need for careful selection of patients. Evidence for use of TH is promising in patients who suffer ventricular fibrillation or pulseless ventricular tachycardia. However, as found by Oddo et al, patients with prolonged resuscitation efforts (beyond 30min) before ROSC can be achieved have a low probability of favorable neurological outcome regardless of TH use, a finding later confirmed by other studies (figure 7). [34, 35] In addition, no difference in overall complications between study and control groups has ever been shown to be statistically significant, suggesting a relatively safe intervention. [31, 33, 34, 35] Although ideal means of cooling and duration of therapy have yet to be identified, it appears that use of TH for select patient groups can promote very favorable neurological outcomes with little risk of complications.

Figure 7



CONCLUSIONS

Despite favorable and promising results that have been achieved with a number of different technologies in small studies, there is still a large demand for definitive therapies to improve the unsatisfactory outcome of only 3% survival from out-of-hospital and 8.2%-22% survival from in-hospital cardiac arrest. [29] It is likely that a combination of several treatments, both basic and advanced, will yield the greatest improvement in outcome. A recent single study report has investigated promising results with the effect of using immediate hemofiltration after out-of-hospital cardiac arrest as a means to improve outcome. [36] Other research has explored the use of IV beta-blockade during a refractory ventricular fibrillation as a means to improve long-term survival but have yet to be investigated in human studies. [37] Additionally, more studies will need to be conducted on already promising findings with TH and E-CPR for cardiac arrest. As of now, successes with these advanced technologies continue to be highly dependent on careful patient selection. In the interim, it is clear that the most simple and inexpensive therapies, such as quality basic life support and rapid successful defibrillation, are the solution to improving survival for cardiac arrest.