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Does the Use of Extracorporeal Cardiopulmonary Resuscitation Improve Neurologically Favorable Survival in Patients with Refractory Out-of-Hospital Cardiac Arrest?

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Abstract:

In this retrospective review, the use of extracorporeal cardiopulmonary resuscitation (ECPR) using extracorporeal membrane oxygenation (ECMO) was assessed in the management of refractory ventricular fibrillation (VF) and ventricular tachycardia (VT) out-of-hospital cardiac arrest (OHCA). Multiple factors were evaluated such as the duration of manual or mechanical cardiopulmonary resuscitation (CPR), ECPR protocols and the rate of favorable neurologic outcomes for these OHCA patients. Survival with a favorable neurologic outcome is defined as cerebral performance categories (CPC) 1 or 2. Although CPR remains and will continue to be a critical component in the management of cardiac arrest, the persistently high mortality rate of the condition warrants further intervention. Established ECPR protocols include timely administration of emergency intervention, patient inclusion and exclusion criteria, mechanical CPR, specific cannulation technique, percutaneous coronary intervention (PCI), as well as post-catheterization lab management. These protocols have shown encouraging initial results with an increased rate of survival with a favorable neurologic outcome when compared to management of similar patients with conventional CPR alone. This literature review found that there is strong evidence supporting the use of ECPR with ECMO support in the management of refractory VF/VT OHCA. Although there exists the need for more randomized control trials, implementation of ECMO and ECPR programs have shown to improve neurological outcomes for these patients.

Introduction:

Cardiac arrest is one of the deadliest public health problems affecting the world today. Approximately 400,000 people in the United States suffer out-of-hospital cardiac arrest (OHCA) each year.[1] Cardiac arrest is most commonly caused by cardiac disease, such as coronary artery disease (CAD) and other structural heart diseases.[2] Cardiac disease accounts for more deaths annually than colorectal cancer, breast cancer, chronic lower respiratory diseases, cerebrovascular diseases, diabetes, influenza, pneumonia, auto accidents, HIV and firearms combined.[3] Patients suffering from OHCA rely heavily on immediate cardiopulmonary resuscitation (CPR) efforts to achieve return of spontaneous circulation (ROSC). Despite these potential life-saving measures, meager outcomes persist with only 6% of patients surviving to hospital discharge.[4]

Approximately one-third of patients who suffer OHCA present to emergency medical services with a shockable rhythm of either ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT).[5] These patients will undergo advanced cardiovascular life support (ACLS) resuscitative measures with repeated defibrillations and administration of pharmaceutical drugs until ROSC is achieved or until patient is pronounced dead. Although VF and VT are considered the most treatable rhythms in patients with OHCA, most defibrillation attempts do not result in sustained ROSC.[6] When patients in VF/VT do not obtain ROSC after three direct current shocks and administration of 300mg IV/IO amiodarone, the condition is termed refractory VF/VT.[5] The dangers of prolonged cardiac arrest increase significantly with each passing minute. Survival drops below 5% if ROSC is not achieved within 30 to 45 minutes, as standard CPR provides only 10 to 30% of normal blood flow to the heart and 30 to 40% of normal blood flow to the brain. [7,8]

Extracorporeal CPR (ECPR), using extracorporeal membrane oxygenation (ECMO) for hemodynamic support, has recently been shown to enhance survival for patients with refractory VF/VT OHCA, with survival rates as high as 40 to 50%.[8] With ECMO, patients who are unresponsive to conventional resuscitation are provided support as a bridge to recovery, destination, or surgery by stabilizing systemic circulation until the underlying cause of the arrest is managed.[9] The purpose of this literature review is to examine the impact of ECMO and ECPR upon the mortality and neurological outcomes in patients with OHCA.

Methods:

A systematic search was conducted using MEDLINE, PubMed, Google Scholar, and UpToDate. Using the Boolean/Phrase mode and the assistance of a research librarian from Augsburg University, the search was conducted using the terms ECMO OR extracorporeal membrane oxygenation OR ECLS OR extracorporeal life support OR ECPR OR extracorporeal cardiopulmonary resuscitation AND OHCA OR out of hospital cardiac arrest AND refractory AND CPR. Results were limited to those published in the English language from the year 2010 to present. The search was limited to the last 10 years to gather only the most recent research. In addition, the reference lists of retrieved articles were reviewed to identify additional, potentially relevant studies. The search options only included peer reviewed articles that consisted of randomized control trials, clinical trials, observational studies, meta analyses, and review articles.

Background:

First, a brief introduction to OHCA will be discussed along with the current literature that surrounds it, including both CPR and ACLS standard of care. Then a mechanical circulatory device called ECMO and its comparison to standard care in the management of OHCA will be addressed. Finally, the implications of ECPR will be examined to determine the impact it has on the mortality and neurologic outcomes of patients that suffer from OHCA.

Cardiac arrest is the abrupt cessation of heart function and subsequent circulatory collapse, often due to cardiac arrhythmias such as VF or pulseless VT. Cardiac arrest occurring outside of a hospital is one of the leading causes of death in developed countries today.[10] Without proper cardiac function, the heart fails to profuse blood and oxygen to vital organs, most importantly the brain, leading to hypoxic-ischemic brain injury. The aim of the care for patients suffering from cardiac arrest is a neurologically intact survival. Neurologically favorable survival outcomes in patients resuscitated worldwide by emergency services is only 5–15%. Critically dependent factors of neurologically favorable outcomes are time, resuscitation quality, advanced care and the treatment of the underlying cause for the cardiac arrest.[11] Neurologically favorable outcomes are defined as cerebral performance categories (CPCs) 1 and 2.[5] CPC scores are categories ranked 1 through 5 that indicate the level of neurologic function after cardiac arrest. This tool is widely used in the assessment of patients after cardiac arrest to evaluate the patient's functional status and their expected quality of life. CPC scores of 1 or 2 are considered to be favorable as they indicate the patient has sufficient cerebral performance and function, and is able to carry out daily activities, independently. CPC scores of 3 or greater indicate severe cerebral disability with limited cognition and dependence of others for activities of daily living.[12]

When cardiac arrest occurs, the mechanisms of the arrest include ventricular tachyarrhythmia, asystole, or pulseless electrical activity of the heart. Furthermore, ventricular tachy-arrhythmias resulting in cardiac arrest include VF and VT. For cardiac arrest patients, the most frequent cause of death is VT (83%). The most prominent mechanism is VF resulting from untreated VT (62%).[10] As previously stated, VF/VT is a favorable prognostic marker for patients with cardiac arrest, as they are both shockable rhythms. Still, 50% of patients in VF/VT OHCA are refractory to treatment, as they fail to achieve sustained ROSC after 3 defibrillation attempts and administration of 300 mg amiodarone. The likelihood of survival with neurologically favorable outcomes for patients with refractory VF/VT declines with longer duration of standard CPR, dropping below 5% if ROSC is not achieved within 30 to 45 minutes of standard ACLS.[8] These poor statistics for survival suggest the need for a modified approach to OHCA that is refractory to conventional treatment.

There are critical steps that must be taken to increase chances of survival for patients with OHCA. These steps include fast recognition of cardiac arrest, activation of Emergency Medical Services (EMS), early CPR, rapid defibrillation, effective advanced life support and integrated care after cardiac arrest.[13] Though the list of critical steps can seem extensive in a rather emergent situation, the integration of all these components in a short period of time is essential to the survival with a favorable neurologic outcome in these patients. Missing one of these critical steps can be detrimental to this desired outcome. When an individual goes into cardiac arrest, timely bystander recognition of the situation can serve as the most vital to all of these steps because without it, many of the subsequent steps may not take place. First, fast recognition will give the best chance for immediate bystander CPR response, which is critical to improve rates of effective resuscitation and defibrillation, thereby, increasing the likelihood of survival and a favorable neurologic outcome. Fast recognition will also help bystanders to immediately call 911 and mobilize EMS responders to the scene.

In a study that took place at The Alfred Hospital in Melbourne, Victoria, Australia, a protocol was developed for both refractory OHCA and refractory in-hospital cardiac arrest (IHCA). This was a prospective observational study called the CHEER trial (mechanical CPR, Hypothermia, ECMO and Early Reperfusion). One key component of this study was that a shorter time between collapse and arrival to the hospital served as a better prognosis to survival. Median time was 48 minutes for survivors compared to 70 minutes for non-survivors.[14] This emphasizes the need for prompt recognition of cardiac arrest and subsequent EMS activation, bystander CPR and transport to the hospital. When bystander CPR is initiated immediately after the individual stops breathing, chest compressions can supply blood flow to vital organs until ROSC is achieved or other measures are taken. Although VF/VT is a favorable rhythm for defibrillation, the standard of care with CPR and ACLS is not always adequate. When a patient's status is termed 'refractory' to conventional care without ROSC, mechanical circulatory support offers an additional option for survival.

CPR Duration

Multiple studies have shown the amount of time in which a patient receives CPR directly correlates to their chance of survival, as each elapsed minute of resuscitation is independently associated with lower odds of a favorable neurologic outcome at hospital discharge.[8, 15, 16] There is no question of the importance of early conventional CPR. Without conventional CPR, cardiac arrest patients are unable to perfuse vital organs and ultimately decrease their chance of a favorable functional outcome or survival overall.[15] Although CPR is a vital component in the survival process of a patient suffering from OHCA, it is not life-sustaining over longer periods of time. When CPR is prolonged, it can lead to metabolic derangement, which is associated with a reduction in favorable outcomes in terms of overall survival and neurologic favorability[8] (CPC 3 or greater).

In a study on prolonged resuscitation, Bartos et al. found that the body undergoes multiple metabolic changes as the duration of resuscitation increases.[8] This study examined 160 patients from the University of Minnesota ECPR cohort who underwent conventional CPR for refractory OHCA prior to initiation of ECMO. Patients who underwent CPR for 40 minutes or longer showed an overall decrease in arterial pH, increase in arterial lactic acid and $paCO_2$ levels, and an increase in left ventricular wall thickening.[8] As previously stated, standard CPR provides only 10 to 30% of normal blood flow to the heart and 30 to 40% of normal blood flow to the brain.[7] The decrease in arterial pH, increase in arterial lactic acid and $paCO_2$ levels, and the increase in left ventricular size are most likely caused by incomplete perfusion provided by CPR and leads to a collective metabolic imbalance. These additional components can cause further complications on top of the original cause of cardiac arrest. For these reasons, prolonged efforts are not life-sustaining and therefore new strategies must be incorporated.

Another component of refractory OCHA is the use of mechanical CPR devices. Currently, there are two mechanical CPR devices used in the United States. These include the mechanical piston device and the load distributing device. This review will focus on the mechanical piston device called The Lund University Cardiac Arrest System or LUCAS™. The LUCAS™ is a device that applies mechanical chest compressions, via circulating pistons, at a constant rate and depth.[6] This device serves a critical role in OHCA management as it allows emergency services to administer other life saving measures all while the patient receives consistently adequate chest compression. It also serves EMS by not taking another crew member away to administer these compressions. As conventional manual CPR progresses, fatigue sets in regardless of the administrator. Without the LUCAS™, crew members must cycle in and out to ensure maximum efficiency and to not compromise the effectiveness of the resuscitation attempt. Finally, mechanical CPR with the LUCAS™ allows for continuous chest compression even during transport to hospital. Conventional CPR ceases during transport as it would require EMS crew members to be out of their safety harness and put them at risk for injury in the case of an automobile accident.

As mentioned previously, refractory VF/VT OHCA is defined as failure to achieve ROSC with ACLS, including 3 attempted defibrillations and administration of 300mg of Amiodarone. VF/VT is termed as a shockable rhythm as the electrical shock from the defibrillator can restart the heart's rhythm in order to pump effectively. Even though over 20% of OHCA patients show VF/VT as their initial rhythm, it is estimated that over 60% of these patients are refractory to current treatment and never achieve ROSC, or the patient dies before they reach the hospital.[6] In an analysis of CPR duration, Grunau et al. showed that once CPR for patients with shockable rhythms reaches 48 minutes in duration, the probability of survival falls below 1%.[17] In the same study, researchers found that for patients with non-shockable rhythms, that duration was 15 minutes.[13,17]

Similarly, in an analysis of 654 adults who received standard CPR in the amiodarone arm of the ALPS trial (Amiodarone, Lidocaine, or Placebo Study) it was found that of the 34% (218/636) of ALPS patients who underwent CPR for over 40 minutes, none of them survived with neurologically favorable status (CPC 1 or 2).[8,18] Data from the patients in the amiodarone arm of the ALPS trial was extracted from this study, as amiodarone is part of the treatment protocol in compliance with the American Heart Association guidelines for ACLS. Both of these studies had large cohorts, with populations of over 600 subjects each. This helped to draw better conclusions with the data that was represented and show greater statistical analysis when comparing differences within the populations. Both studies showed a significant decrease in likelihood of neurologically favorable survival as CPR was prolonged. Although the ALPS trial did not provide analysis of non-shockable rhythms, the data for shockable rhythms was similar to that of Grunau et al. for the same population.[17,18] These statistics show that with prolonged resuscitation of over 40 minutes, chances of survival with a CPC score of 1 or 2 are drastically low. When refractory VF/VT OHCA is established, if resuscitation efforts are to continue, it is essential to explore other means of management such as ECPR to increase odds of a favorable outcome.

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a form of cardiopulmonary life-support. During ECMO management, blood is drained from the venous system, then circulated outside the body through a membrane oxygenator, which acts as artificial lungs and oxygenates the blood while removing CO_2. The blood then passes through a mechanical pump, which acts as an artificial heart, and reinfuses it into the body to perfuse all organs.[19, 20] There are two forms of ECMO, including veno-venous (VV) ECMO and veno-arterial (VA) ECMO. This literature review will focus on VA-ECMO, as it has the ability to provide both cardiac and respiratory support, as opposed to VV-ECMO, which is used only to support respiratory dysfunction.

When VA-ECMO is used in the management of refractory VF/VT OHCA patients, blood is drained from the femoral vein and reinfused into the femoral artery via a percutaneously placed cannula. This cannulation technique serves as an advantage, as it is rapid and less invasive. This allows it the ability to be performed nearly everywhere, including the emergency room, cardiac catheterization lab, operating room, as well as in the field environment. Once ECMO is running and hemodynamic stability is established, the patient can be transferred with the entire unit.[9] The goal of ECMO is to support the patient as a bridge to recovery, bridge to destination, or bridge to surgery by stabilizing systemic circulation until the heart can recover. Extracorporeal-CPR (ECPR), using ECMO for hemodynamic stability, has been shown to enhance survival for patients with refractory VF/VT OHCA, with survival rates as high as 40% to 50%.[1,5,10,21-23] When a patient is in refractory VF/VT OHCA, time is of the essence. ECPR can provide an opportunity to stabilize these patients so that the cause of the cardiac arrest can be determined and reversed without neurologic deterioration.

In a study at the University of Minnesota, an ECPR protocol was implemented in the management of refractory VF/VT OHCA (UMN-ECPR).[5] Over the first 3 months of this protocol, 27 patients were transferred by EMS for OHCA, 18 of which met inclusion/exclusion criteria. Of these 18 patients, 9 (50%) of them survived with a neurologically favorable outcome (CPC 1 or 2). In a follow-up study, Bartos et al. looked at the outcome of 100 consecutive adult patients with refractory VF/VT OHCA that underwent the same ECPR protocol.[1] Of the 100 transported patients that met inclusion/exclusion criteria, 40 (40%) of them were discharged with a neurologically favorable outcome of CPC 1 or 2, as well as at a 3-month follow-up.[1] This evidence suggests that patients in refractory VF/VT OHCA can benefit greatly from the ECPR protocol used in these studies. In the aforementioned CHEER trial, over a 32-month period, 26 patients (11 OHCA and 15 IHCA) with refractory cardiac arrest were treated with ECMO. Of these 26 patients, 14 (54%) of them survived to discharge with full neurological ability (CPC score 1). This group included 9/15 (60%) IHCA patients and 5/11 (45%) OHCA patients.[14]

When comparing the UMN-ECPR protocol to conventional CPR of 170 patients meeting the same criteria and treated by the same EMS units, the ECPR protocol showed a much higher rate of favorable neurologic survival to discharge with CPC 1 or 2.[5] As mentioned previously, in the patients treated with ECPR protocol, 9/18 (50%) survived with a favorable neurologic outcome, while only 14/170 (8.2%) patients treated with conventional CPR survived with a favorable neurologic outcome.[21] In a study from Japan, neurologic outcomes of OHCA patients following management with either ECPR protocol or conventional CPR were compared.[22] 454 patients met inclusion/exclusion criteria, including 260 patients in the ECPR group and 194 patients in the non-ECPR group. Results of this study showed the ECPR management group to be superior for favorable outcomes (CPC 1 or 2) in comparison with the conventional CPR group. At the 1-month follow up, rate of favorable outcomes were 12.3% in the ECPR group and 1.5% in the conventional CPR group. At 6-months, ECPR patients had a rate of 11.2% compared to 2.6% with the conventional CPR group. In another study, Wang et al. conducted a prospective observational study to compare the use of ECPR in patients with OHCA and patients with IHCA. Over 5 years, 31 patients were treated with the ECPR protocol for OHCA. In this OHCA group, the overall survival was 38.7%, with a favorable neurological outcome of 25.8%.[23] These studies provided evidence that implementation of an ECPR protocol for the management of OHCA could serve to improve survival with a favorable neurologic outcome.

ECPR Protocol Inclusion and Exclusion Criteria

Inclusion and exclusion criteria differed across all studies researched in this review. Though similar, each study had specifics that narrowed the patient population in which they treat with their prospective protocol. The UMN-ECPR study had the most extensive criteria of all the studies analyzed. Inclusion criteria included: 1) OHCA with presumed cardiac etiology cardiac arrest; 2) first presenting rhythm was shockable (VF or VT); 3) age 18 to 75 years; 4) received at least 3 direct current shocks without sustained ROSC; 5) received amiodarone 300mg; 6) body could accommodate a LUCAS automated CPR device and 7) transfer time from the scene to the cardiac catheterization lab (CCL) of less than 30 minutes. Exclusion criteria included: 1) ROSC before 3 shocks were delivered; 2) Nursing home residents; 3) Do Not Resuscitate (DNR)/Do Not Intubate (DNI) orders in place; 4) known terminal illness (eg, cancer, end-stage liver, kidney, or heart disease); 5) traumatic arrest; 6) pulseless electrical activity and asystole; 7) significant bleeding and 8) manual CPR as the only option. In addition to this inclusion/exclusion criteria, any patient with ≥1 of the following was declared dead on CCL arrival: 1) end-tidal $CO_2 < 10$ mmHg; 2) $PaO_2 < 50$ mmHg; 3) lactic acid >18 mmol/L; and 4) time from EMS activation to CCL arrival >90 min. For patients that met inclusion/exclusion criteria, UMN-ECPR protocol called for the immediate transfer to the University of Minnesota while incorporating mechanical CPR with the LUCAS device en route. Upon arrival, patients were sent to the CCL where interventional cardiologists connected them to ECMO.[5]

In the CHEER trial, the inclusion criteria included: 1) patients 18-65 years of age; 2) cardiac arrest due to suspected cardiac etiology; 3) chest compressions commenced within 10 minutes by bystanders or EMS; 4) initial cardiac arrest rhythm of VF and 5) mechanical CPR device available. Patients were deemed as in refractory cardiac arrest after 30 minutes of CPR with no ROSC. If the above criteria were met, OHCA patients were transported to Alfred Hospital while receiving continuous mechanical CPR and infusion of 2 L of cold saline en route. Upon arrival to the emergency room, two critical care physicians connect the patient to ECMO. Once patient is hemodynamically stable, suspected cause of cardiac arrest is analyzed and treated and patient is sent to the intensive care unit (ICU).[14]

The next study reviewed was a large prospective observational study from Japan that observed neurological outcomes of OHCA patients following management with either ECPR protocol or conventional CPR/non-ECPR protocol. Inclusion criteria included: 1) VF/VT on initial ECG; 2) cardiac arrest on hospital arrival with or without pre-hospital ROSC; 3) within 45 minutes from onset of cardiac arrest to hospital arrival; 4) no ROSC within 15 minutes after hospital arrival and 5) age of 20-74 years. Exclusion criteria included: 1) poor activity of daily living prior to cardiac arrest; 2) non-cardiac origin; 3) core body temperature below 30°C and 4) if patient did not have informed consent from individuals representing them.[22]

In the final study evaluated for this review, Wang et al. conducted a prospective observational study to compare the use of ECPR in patients with OHCA and patients with IHCA over a 5-year period. OHCA inclusion/exclusion criteria differed for IHCA and OHCA patients in this study. For OHCA patients, eligibility was considered if; 1) the arrest was witnessed; 2) conventional resuscitation was started within 6 minutes and 3) CPR was continued during transportation. Other exclusion criteria were: 1) OHCA of a traumatic origin; 2) preexisting multiple organ dysfunction; and 3) sustained ROSC for more than 20 min after OHCA.[23]

When comparing the criteria in which these studies used to decipher between ECPR treatment vs. conventional CPR treatment, there were many similarities and differences across the studies evaluated. First, all but 1 of the studies mentioned the need for VF or VT to be the initial heart rhythm. This is in line with what has been previously discussed in that VF and VT are shockable rhythms and carry a better prognostic factor than that of asystole and PEA, or non-shockable rhythms. Next, all but 1 of the studies included the presumption of the cardiac arrest being of cardiac origin in their criteria. This factor holds importance because if it is of cardiac origin, this narrows the presumed treatments and PCI in the CCL will be more beneficial. Finally, all but the study from Japan mentioned the need for continuous CPR in their criteria. Continuous CPR serves an important role in the management of OHCA as this helps to consistently perfuse vital organs in the time that the heart has stopped pumping on its own. These 3 studies also mentioned the importance of rapid CPR/ACLS upon onset of cardiac arrest. Without rapid response and continuous CPR, ischemic injury to these organs can cause serious dysfunction and eventually death.

These studies also had many differences. The first way in which they differed was in the complexity of each study's criteria. The UMN-ECPR criteria is longer than the others, especially that of Wang et al., each having 15 specific inclusion/exclusion criteria and 6 specific inclusion/exclusion criteria, respectively. Also, the CHEERS trial did not specify any exclusion criteria at all. Secondly, 2 of the studies mentioned specific time constraints in which the patient must be transferred to the hospital/CCL. The UMN-ECPR study inclusion criteria states that time of transport from the scene to CCL must be 30 minutes or less. This ensures that as long as the patient meets all inclusion criteria, they can be treated with PCI before extensive deterioration. The study from Japan requires the time from initial onset of cardiac arrest to the hospital be less than 45 minutes. This inclusion factor is in line with previously stated information that after 40-45 minutes of conventional CPR, survival with a favorable neurologic outcome declines drastically. Lastly, though similar, 3 out of the 4 studies mentioned had age ranges for patients that could receive treatment included in their inclusion/exclusion criteria. This factor is significant in that these small differences in age brackets can decide whether or not ECPR protocol will be administered. When looking only at the age of a OHCA patient and not at any other prognostic markers, whether patients at the low and high ends of these ranges receive treatment is dependent on which protocol is being used.

The breadth of these inclusion and exclusion criteria serve an important role in each study's protocol. Criteria is based on research to give the best chance for survival with a favorable neurologic outcome in patients who receive the treatment. Without this criteria, time, money and resources could be used on patients whom are unlikely to survive with favorable neurologic outcomes. As always, it is up to EMS and providers to use clinical judgement to assess overall likelihood of a favorable outcome, as a single factor does not always carry the same weight from patient to patient. For example, a healthy 26-year-old with a lactic acid of 20 mmol/L may have a better chance of a favorable outcome than an unhealthy 74-year-old with the same lactic acid level. This criteria must be assessed immediately upon arrival by EMS as shorter time from initial cardiac arrest to CCL/hospital is associated with more favorable outcomes.

Discussion:

The persistently high mortality rate associated with OHCA calls for a need for intervention. Conventional CPR, albeit very important to the overall outcome, does not always provide sufficient perfusion to vital organs in order to obtain a favorable neurological outcome, especially when it is prolonged in such cases as refractory VF/VT OHCA. The main purpose of this literature review was to analyze the impact of ECPR for the treatment of refractory VF/VT OHCA. Through the research analyzed in this review, it was found that there are many factors that play a role in the successful outcome of these patients. This review focused on the components of CPR duration, ECPR protocol and survival with a favorable neurologic outcome.

CPR Duration:

Through this literature review, it was concluded that as the duration of conventional CPR is prolonged, rate of survival with a favorable neurologic outcome declines.[8, 15] In a randomized controlled trial, Reynolds et al. analyzed CPR duration in patients with EMS-treated OHCA. It was found that with conventional CPR, 90% of subjects with a favorable neurologic outcome obtain ROSC within 20 minutes, and 99% obtain ROSC within 37 minutes. With these numbers, it is unclear as to when resuscitation efforts should be continued or be terminated. Prolonged conventional CPR can also have detrimental metabolic effects on the body.[8] In a similar study mentioned previously, Grunau et al. compared OHCA patients with initially shockable rhythms to OHCA patients with non-shockable rhythms. In terms of survival with a favorable neurologic outcome, the findings in this study heavily favored patients with initially shockable rhythms. Another factor in this study that increased odds of survival with a favorable neurologic outcome was age. When younger patients went into cardiac arrest, it was found that a higher percentage were able to survive with favorable neurologic outcomes as conventional CPR was prolonged.

Another study compared the rate of survival in relation to the duration of CPR in 2 groups of patients with refractory VF/VT OHCA. 1 group was treated with an ECPR protocol and the other group was treated with conventional CPR. The ECPR group showed significantly greater rates of survival with a favorable neurologic outcome in all cases in which CPR lasted longer than 20 minutes. Similar to the previously mentioned studies, of the 218 patients in the conventional CPR group that received CPR for over 40 minutes, none survived with a favorable neurologic outcome (CPC 1 or 2). In comparison, of the 36 patients in the ECPR group that received conventional CPR for 50-59 minutes followed by ECMO, 9 of them (25%) survived with a favorable neurologic outcome and 19% of patients survived with a favorable neurologic outcome even after 60 minutes or greater of conventional CPR followed by ECMO.[8] Most likely, there are factors that differentiate patients chosen for ECPR and those not. However, there were no survivors in the group who received conventional CPR which makes it difficult to argue that this is an effective strategy once the duration of conventional CPR reaches 40 minutes. This study shows that even after prolonged resuscitation attempts occur, at durations when conventional CPR fails to keep the patient alive, ECPR protocol still shows benefit in survival with a favorable neurologic outcome.

Although these studies focused on the duration of conventional CPR, there were several other factors that will affect the survival with favorable neurologic outcomes in patients treated with ECPR. Some of these factors include; no-flow time, causes of arrest, refractory arrest or re-arrest, and post-resuscitation care.[24] While conventional CPR still holds true as an essential part of the initial management of OHCA, the duration at which it can adequately sustain life is undetermined. Although these studies do not necessarily construct a maximum time limit at which conventional CPR should be terminated, they can help to guide conventional CPR in terms of minimum duration. When evaluating these numbers in terms of conventional CPR duration and the likelihood of survival with a favorable neurologic outcome, these studies suggest the need for additional intervention at a certain duration to increase the chances of survival with CPC 1 or 2. ECPR is associated with improved survival with a favorable neurologic outcome for patients with shockable OHCA compared with conventional CPR at all durations of time less than 60 minutes. Also, it may allow successful treatment of patients receiving prolonged conventional CPR up to 60 to 98 minutes, but not without the risk of survival with an unfavorable neurologic outcome.[8] Termination of conventional CPR without additional treatment leads to subsequent death in cardiac arrest patients. This termination of resuscitative attempt is predicated by EMS members when they feel these attempts become futile. If additional intervention is available, this termination of resuscitative efforts may be delayed, and inevitable death will be avoided for the time being with possible ROSC due to continued resuscitative efforts, or with ECPR.

ECPR Protocol:

When a patient suffering from VF/VT OHCA is deemed refractory to conventional ACLS management, there are three options; continue current management indefinitely until ROSC is achieved, call for termination of resuscitation and subsequent death, or transport to ECMO enabled medical facility for life saving measures. In multiple studies, ECPR protocol using ECMO for hemodynamic stability has recently been shown to enhance survival with a favorable neurologic outcome for patients with refractory VF/VT OHCA.[1,14,16,21,22] In these patients, the ECPR protocol stabilizes perfusion regardless of the patient's cardiac rhythm. ECPR provides hemodynamic support, which in turn, stops the progression of ischemic injury prior to ROSC, allows time to regulate metabolic instability, and provides time to treat the underlying cause of the refractory cardiac arrest.[8] For each patient that is considered for ECPR, there are specifications that must be met in order to receive the treatment. The inclusion and exclusion criteria discussed previously is the basis of which patients are treated with ECPR protocol and which ones are not. ECPR protocols differed slightly across studies, but maintained many similarities to draw conclusions from. Overall, the main factors included within each article to best predict likelihood of survival with a favorable neurologic outcome after prolonged resuscitations were; 1) initial shockable cardiac rhythm; 2) bystander CPR; 3) witnessed cardiac arrest and 4) OHCA being of cardiac origin.[1,5,14,22] Meeting inclusion and exclusion criteria plus these key features warrant early consideration of novel therapies such as ECPR.

Through all the research evaluated for this literature review, early recognition and subsequent bystander or professional conventional CPR initiation was the most important factor in successful outcomes. There are some elements of OHCA that can be overcome by ACLS and ECPR, but cerebral hypoxia/anoxia carries a severely high mortality rate and is the main cause for death in these patients.[11] Not only is early recognition of cardiac arrest important, but early recognition by EMS of cardiac arrest which is refractory to conventional treatment carries extremely high importance in the ECPR protocol. Like conventional CPR, time is of the essence with ECPR as well. If these patients are not transported and started on ECMO in a timely manner, CCL activation and treatment may not be enough to offer benefit.[21] The time in which conventional CPR should be stopped and ECPR protocol initiated is somewhat unclear. Studies outlined in this review show that prolonged conventional CPR is associated with a poorer outcome, so it would be advantageous to initiate ECPR at an earlier time. Kim et al., proposed that the ideal cut-off time to switch from conventional CPR to initiate ECPR is 21 minutes.[24] This allows enough time for the patient to be transported and cannulated in a shorter amount of time from the onset of cardiac arrest. This stresses the importance to have clear guidelines in place along all levels of ECPR protocol from local EMS all the way to interventional cardiologists as ECPR requires a well-organized, succinct team effort.

Throughout this review, many benefits of ECPR have been discussed. These benefits, however, must be considered along with the significant risks in the decision to institute ECPR on refractory OHCA patients. Bleeding is the most frequent and most serious complication associated with ECPR support.[25] The cannulation technique used in most cases for VA-ECMO is through the femoral artery and vein. This procedure, if not done correctly, can have detrimental effects on the outcome of these patients. Studies in this review differed in who performed the cannulation. In the UMN-ECPR protocol, Yannopoulos et al. reported cannulation of femoral artery and vein was performed with percutaneous technique and ultrasound guidance. This study emphasized the importance of this procedure and the need for interventional cardiologists to perform it.[5] In the CHEER-ECPR protocol, upon arrival to the emergency room, mechanical CPR is paused, and two critical care physicians connect the patient to ECMO using percutaneous cannulation of the femoral vessels.[14] The UMN-ECPR protocol reported 2 complications in which patients had moderate bleeding around the cannulation site, this was controlled with the decrease in anticoagulation therapy. The CHEER-ECPR protocol reported the need for blood transfusion in 16 of the 26 patients treated with ECMO. They also reported that 2 patients died primarily of major bleeding complications. These 2 studies show drastic differences in both the rate and severity of bleeding complications and it highlights the importance of who is performing the cannulation procedure. Depending on the level of training the critical care physicians from the CHEER-ECPR protocol had in this process, one could theorize the importance of advanced training. Interventional cardiologists have specialized training in techniques such as this, which may help to limit complications.

Neurologic Outcomes:

Six studies examined the outcome of patients that were treated with ECPR in the event of VF/VT refractory cardiac arrest. [1,14,16,21-23] The primary outcome of these studies was defined as neurologically favorable survival (CPC 1 or 2). In each of these studies, VF/VT refractory OHCA patients treated with ECPR protocol showed superior outcomes when compared to the same population of patients treated with conventional CPR alone. Each study mentioned factors that were associated with survival with a favorable neurologic outcome. First, rapid EMS response time and shorter time from 911 call to CCL. As discussed previously, prolonged CPR is associated with higher mortality. It was concluded that faster initiation of ECPR lead to better outcomes. Secondly, cardiac arrest in a public place followed by rapid bystander CPR is essential to the overall success of ECPR. Although it was not shown to not be as proficient as ECPR, early bystander conventional CPR plays a critical role to initiate the reperfusion process after the onset of cardiac arrest. Limiting the time in which there is no blood flow may be the biggest factor in association with decreasing likelihood of ischemic brain injury. Lastly, evidence of reversible coronary artery disease can improve outcomes because it allows for providers the chance to use PCI to resolve the defect that is causing the cardiac arrest.[26]

Many of the studies analyzed in this review focused on the survival with a favorable neurologic outcome. The other side of this spectrum of outcomes would be death, as well as survival with an unfavorable neurologic outcome (CPC 3 or greater). Obviously, when given the choice of survival with a favorable neurologic outcome and death, the former is the easy choice in most cases. When favorable neurologic status is not definite, this can become a question of ethical debate. As mentioned previously, a CPC score of 3 or greater indicates severe cerebral disability with limited cognition and the dependence of others for activities of daily living.[12]

When a patient suffering from OHCA does not have any of the factors listed in the previous paragraph and the duration of conventional CPR is drawn out, there is an increase in the chance for survival with an unfavorable outcome. Bartos et al. reported the risk of survival with a CPC score of 3 or greater increased to 9% (3 of 35) at 60 to 69 minutes of conventional CPR.[8] While it is easy to look at some of these statistics and see any increase in likelihood of survival as an encouraging marker, it is important to evaluate the quality of life and the chance this patient may not recover from this unscathed. These are the risks that must be weighed when considering a patient for ECPR management in the setting of OHCA after prolonged resuscitation efforts have not served beneficial.

Limitations

There were limitations found within each article. First, the sample size was extremely small for several studies which examined the use of ECPR protocol in the treatment of refractory VF/VT OHCA. Many studies had 100 or less patients, which makes it difficult to form overall conclusions that can be applied to large populations. In addition to small sample sizes, quality of treatment among facilities could vary. Some of the observational studies assessed multiple hospitals and medical facilities. This variability in treatment protocols and management strategies could alter outcomes within different populations. Also, many of these protocols had criteria that narrowed the patient population that was treated. VF and VT are both shockable rhythms and have greater implications for survival than asystole and pulseless electrical activity (PEA), which are considered non-shockable rhythms. By excluding patients with non-shockable rhythms from the treatment cohort, numbers could be skewed to show improved survival rate as patients in VF/VT already have a higher chance of survival. In contrast, if all asystole and PEA patients are placed into the compared cohort, their decreased chance of survival will negatively skew mortality rate. Finally, the ethical dilemma to perform randomized control trials on refractory VF/VT OHCA patients causes difficulty in drawing conclusions. These critically ill patients need effective treatment for survival and it would be unethical to not provide life-saving treatment if it is available.

Conclusion:

While conventional CPR remains essential in the management of OHCA, ECPR using ECMO has proven to be effective in improving survival with favorable neurologic outcomes in patients suffering from refractory VF/VT OHCA. ECPR is able to provide hemodynamic support to patients that cannot provide it for themselves and gives medical providers the ability to diagnose the underlying cause of the cardiac arrest, all while maintaining perfusion and sustaining neurologic function. The persistently high mortality rate in this patient population calls for an intervention and several studies have shown the survival benefit that ECPR provides. These studies concluded that major factors that improve outcomes are timely recognition and prompt EMS response, rapid bystander CPR, evidence of reversible coronary artery disease and shorter duration of time from initial arrest to the CCL. The longer a patient is without cardiac function, the greater chance of mortality and unfavorable neurologic outcomes (CPC 3 or greater). If the heart is unable to pump blood throughout the body and CPR is inefficient in doing so, ECPR is the next best step in providing life-saving management.

Each step in this process weighs heavily on a system-based protocol in which an entire team must be involved for a successful outcome. In the studies evaluated in this review, a specific system was in place to expedite the entire process. This efficiency can be the difference between life and death for some patients. There exists a need for these protocols to be implemented into a greater number of medical systems. This would allow for exposure to a larger patient population and in turn, decreased mortality rates. Although there is a brevity of research on exact implementation of specific protocol, the current studies show encouraging numbers. With continued research on this topic, exact protocols can be assessed and reconfigured to best serve the patient including personnel, equipment, logistics and collaboration with EMS.

In a proposed randomized control study from 2012, Belohlavek et al. randomized patients into a control arm in which standard care was used to treat OHCA without ROSC and to a "hyperinvasive arm" in which the patient was immediately connected to mechanical chest compression and transported to a medical center for the initiation of ECPR.[11] This study is still ongoing without current results, but it does propose a different approach to studies around OHCA. This study will help to answer some of the questions and decrease some of the limitations involved with other observational studies. Since ECPR is not the first line treatment for refractory OHCA and there are no guidelines stating the need for ECPR in the treatment of all OHCA, standard care with conventional CPR and ACLS measures still offer life-saving treatment. This study will also help to answer questions on the implications of ECPR and how it can be definitively used over a wider patient population in the management of refractory OHCA. The randomization process serves as a control to limit bias and it provides a way in which cause-effect relationships can be determined.

All protocols researched in this review have shown improved neurologic outcomes when compared to conventional CPR alone. Randomized control trials are difficult in this critical condition, as not providing life-saving therapy when it is available would be unethical. ECPR offers therapy in the management of refractory cardiac arrest with numerous studies now showing a survival benefit. Providing patients with access to ECPR in a timely manner involves a community-wide approach in both the in-hospital and out-of-hospital setting. Continued research is needed to increase the number of patients treated and in turn, provide better clarification to protocol and specific practices that can continue to decrease the mortality rate and improve neurologic outcomes in a condition that has had a high mortality rate for too long.

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