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REVIEW ARTICLE

Refractory Out of Hospital Cardiac Arrest

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Abstract: Refractory out of hospital cardiac arrest is a common problem that is associated with poor overall survival rates and neurological outcomes. There are various definitions that have been used but the most accepted one is cardiac arrest that requires more than 10 minutes of Cardiopulmonary Resuscitation (CPR) efforts or more than 3 defibrillation attempts. There have been different pharmacologic and non-pharmacologic therapies that were studied in these patients. None of the antiarrhythmic or vasopressor medications have been consistently shown to improve survival or neurological outcomes in this subset of patients. This has led to the introduction of various devices aimed at improving outcomes such as mechanical CPR devices, Extracorporeal Cardiopulmonary Resuscitation (ECPR), targeted temperature management and early invasive approach. There is accumulating evidence that there seems to be an improvement in outcomes when these devices are used in refractory cardiac arrest patients. But none of these devices have been shown to improve outcomes when used in isolation. This underscores the importance of systematic approach to these complex patients and using these therapies in combination. There has been a paradigm shift in the approach to these patients. Instead of repeated and prolonged CPR attempts in the field, it is suggested that these patients need to be moved to cardiac arrest centers with a mechanical CPR device in place, so a percutaneous Extracorporeal Membrane Oxygenator (ECMO) can be placed to "buy" time for other therapies such as therapeutic hypothermia and early coronary angiography followed by intervention as indicated. Careful selection of patients who might potentially benefit from this approach is critical to the success of these programs.

Keywords: Cardiac arrest, Cardiopulmonary Resuscitation (CPR), neurological outcomes, survival rates, extracorporeal membrane oxygenator, defibrillation.

1. INTRODUCTION

It is estimated that in the United States (US) Out of Hospital Cardiac Arrest (OHCA) accounts for over 350 000 deaths annually. There are a number of challenges in examining the epidemiology of cardiac arrest in the US due to lack of standards for monitoring the incidence and outcomes. Despite significant advances in treatment, survival to hospital discharge in patients with cardiac arrest is still low at 11.4% [1]. In hospital cardiac arrest is associated with equally high mortality rates [2]. Slightly over 20% of OHCA patients present with a shockable rhythm initially (ventricular fibrillation, VF or pulseless ventricular tachycardia, VT) [1]. Even though VF and pulseless VT is regarded as the most treatable rhythm in patients with OHCA, it is well established that most defibrillation attempts do not result in sustained Return of Spontaneous Circulation (ROSC) [3]. There is an inverse relationship between the duration of VF/ VT and resuscitation outcome [4, 5]. A particularly unique problem is refractory cardiac arrest when ROSC is not achieved despite Advanced Cardiac Life Support (ACLS). This is often seen in patients with profound metabolic acidosis, pulmonary embolism or acute coronary occlusion [6]. It is estimated that greater than 60% of patients with VF or pulseless VT OHCA are refractory to current treatment and never achieve ROSC or die before they reach the hospital [7]. American Heart Association (AHA) 2015 ACLS guidelines recommend continuing resuscitation efforts for 30 to 45 minutes in patients with refractory cardiac arrest, until they either achieve ROSC or pronounced dead. Refractory cardiac arrest is defined as the lack of ROSC after 30 minutes of appropriate cardiopulmonary resuscitation in the absence of hypothermia. Refractory ventricular fibrillation on the other hand has various definitions including: VF persisting despite three shocks [8] or a combination of three unsuccessful shocks and amiodarone [9]. Regardless of the definition used, this cohort of patients presents a unique therapeutic challenge and have high mortality rates. The purpose of this review is to understand the problem of refractory ventricular fibrillation and available novel therapies for these patients.

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2. ETIOLOGY FOR REFRACTORY ARREST

As one might suspect Coronary Artery Disease (CAD) with acute ischemia is a common cause for cardiac arrest. These patients seem to benefit from revascularization [10]. The 2015 AHA guidelines for CPR and emergency cardiovascular care accordingly issued a class I, LOE B-NR recommendation for emergent coronary angiogram and PCI for patients with OHCA and ST Elevation Myocardial Infarction (STEMI) noted in the post resuscitation ECG. Evidence is less clear in patients without obvious ST elevation, AHA guidelines recommend emergent coronary angiogram for selected patients with OHCA who are comatose with electrical or hemodynamic instability (class IIa LOE B-NR) [11]. Until recently the prevalence of CAD was unknown in patients with refractory VF OHCA. In a recently published study by Yannopoulos *et al.*, significant coronary artery disease (>70% stenosis) was noted in greater than 80% of patients with refractory VF OHCA of which about 60% were acute thrombotic lesions. This study also showed better neurological outcomes in patients who underwent revascularization underscoring the importance of CAD and its treatment in refractory VF patients [12].

3. PARADIGM SHIFT

Traditionally patients with refractory OHCA have ACLS resuscitation measures performed in the "field" with repeated defibrillations and pharmacotherapy until ROSC is achieved or when continued resuscitation is considered medically futile. However, with newer technologies such as mechanical CPR and Extracorporeal Life Support (ECLS) therapy there is a push toward transporting patients with refractory VF to the closest facility that can offer such advanced therapies. In other words, it is suggested by experts that instead of the traditional "stay and play" approach, we should move to "load and go" strategy. There are some unanswered questions at this time with a "load and go" strategy such as – how long does one continue the ACLS protocol before a decision is made to move the patient with a mechanical CPR device to the closest hospital or when does one consider stopping resuscitation efforts in the field due to medical futility. The 2015 AHA guidelines for CPR issued a class IIb – LOE B-NR for mechanical CPR devices to be used in select situations where delivery of manual CPR may be difficult or dangerous such as in the ambulance, cardiac catheterization lab or need for prolonged CPR with limited rescuers. Extracorporeal CPR or ECLS can be considered in select patients with refractory cardiac arrest as an alternative to prolonged CPR when there is suspicion for a potentially reversible cause of cardiac arrest (class IIb – LOE C-LD) [13].

4. PHARMACOLOGIC TREATMENT FOR REFRACTORY VF ARREST

Antiarrhythmic drugs such as lidocaine, amiodarone, nifekalant and vasopressors like epinephrine are commonly used during resuscitation of cardiac arrest patients. Overall there is limited evidence supporting the use of these medications, but in patients with refractory arrest it is unclear if they are beneficial. Amiodarone given in combination with epinephrine after 3 failed defibrillations was shown to improve survival to hospital admission compared to placebo. However, there was no improvement in survival to hospital discharge or favorable neurological outcomes with amiodarone use [14]. Lidocaine did not improve ROSC or survival to hospital discharge rates in refractory arrest patients [15, 16]. Lidocaine was inferior to amiodarone in improvement of ROSC and survival to hospital admission rates, but neither one of these drugs were beneficial in improving survival to hospital discharge rates or favorable neurological outcomes [17]. A recently published study randomized over 3000 patients with OHCA to amiodarone, lidocaine or placebo and demonstrated that there was no significant improvement in survival to hospital discharge rates or favorable neurological outcomes with either amiodarone or lidocaine compared to placebo. [18]. Procainamide was tried in refractory VF OHCA victims that received more than 3 shocks and IV lidocaine. There was no improvement in ROSC rates, survival to hospital admission or discharge rates with procainamide and hence this drug quickly fell out of favor [19]. Magnesium was thought to be helpful in refractory VF/ pulseless VT OHCA patients, due to its role in regulating sodium, potassium and calcium flow across cell membranes. Two randomized trials examined the use of magnesium in patients with refractory VF arrest and demonstrated no benefit in ROSC rates, survival to hospital admission or discharge rates [20, 21]. Accordingly, the 2015 AHA guidelines on CPR issued a class IIb LOE B-R for amiodarone and class IIb LOE C-LD for lidocaine as an alternative to amiodarone in OHCA patients with VF/ pulseless VT that is refractory to CPR, defibrillation and vasopressor therapy [13]. The role of epinephrine in OHCA patients has been controversial. Due to its effects on cerebral and coronary perfusion pressures, epinephrine use in cardiac arrest patients made theoretical sense. A randomized placebo controlled trial showed improved ROSC and survival to hospital admission rates with epinephrine use in OHCA victims, but there was no difference in long term outcomes such as survival to hospital discharge or favorable neurological recovery rates [22]. A recently published trial compared amiodarone, lidocaine and placebo in refractory VF or pulseless VT OHCA patients. This trial showed no significant difference in survival to hospital discharge or favorable neurological outcomes with these medications compared to placebo [18].

5. MECHANICAL CPR DEVICES IN REFRACTORY ARREST

Mechanical CPR devices were introduced with the hope that this would be better than manual CPR as there is a predictable level and rate of chest compressions and this also frees up the rescuer to perform other critical resuscitation activities. Currently there are two different kinds of devices available in the United States (US): mechanical piston device and load distributing device. The Lund University Cardiac Arrest System (LUCAS™ is a gas or electric powered piston device that is positioned on the sternum and produces a consistent chest compression rate and depth. The pilot study randomized close to 150 OHCA patients to LUCAS or manual compression. This study failed to show any significant difference in early survival or survival to hospital discharge in LUCAS™ arm [23]. Following this, 2 large randomized trials examined the use of LUCAS™ device in cardiac arrest patients. The PARAMEDIC (pre-hospital randomized assessment of a mechanical compression device in cardiac arrest) trial randomized over 4000 patients with OHCA to either LUCAS™ mechanical CPR or manual CPR but did not show any significant difference in 30-day survival in the LUCAS™ arm [24]. The LINC (LUCAS In Cardiac arrest) trial randomized around 2500 patients to LUCAS™ or manual CPR and showed no difference in 4-hour survival, survival to hospital discharge or favorable neurological outcomes with the LUCAS device [25]. A Meta-analysis of the 3 randomized trials using LUCAS device showed similar results. Fig. (**1**) summarizes the results of this metanalysis.

There were other mechanical piston devices that were tested in small studies without any significant benefit over manual CPR.

The Load Distributing Band (LDB) device is a circumferential vest that works similar to a blood pressure cuff, and is composed of a pneumatically or electrically actuated constricting band and backboard. Autopulse™ device belongs to the LDB category and had encouraging results in smaller studies at first [26-28]. A multicenter trial that randomized over 1000 patients to either mechanical CPR using the Autopulse™ device or manual CPR demonstrated no improvement in survival to 4 hours, or survival to hospital discharge or favorable neurological outcomes in the mechanical CPR arm. Moreover there was a trend toward worse survival and neurological outcomes in the mechanical CPR group that was felt to be related to lack of experience with this device [29]. Accordingly the 2015 AHA guidelines for CPR issued a class IIb LOE B-R for these mechanical CPR devices as a reasonable alternative to manual CPR by trained professionals when manual CPR is not possible or considered dangerous [30].

6. EXTRACORPOREAL CPR

Extracorporeal CPR (ECPR) or Extracorporeal Life Support (ECLS) refers to placement of veno arterial Extracorporeal Membrane Oxygenation (ECMO) device in patients with refractory cardiac arrest. ECMO has been established as a hemodynamic support device in patients with refractory cardiopulmonary failure. The use of this modality in patients with refractory cardiac arrest was initially suggested in 1966 for patients with cardiac arrest, but was limited in due to lack of adequate vascular access, need for

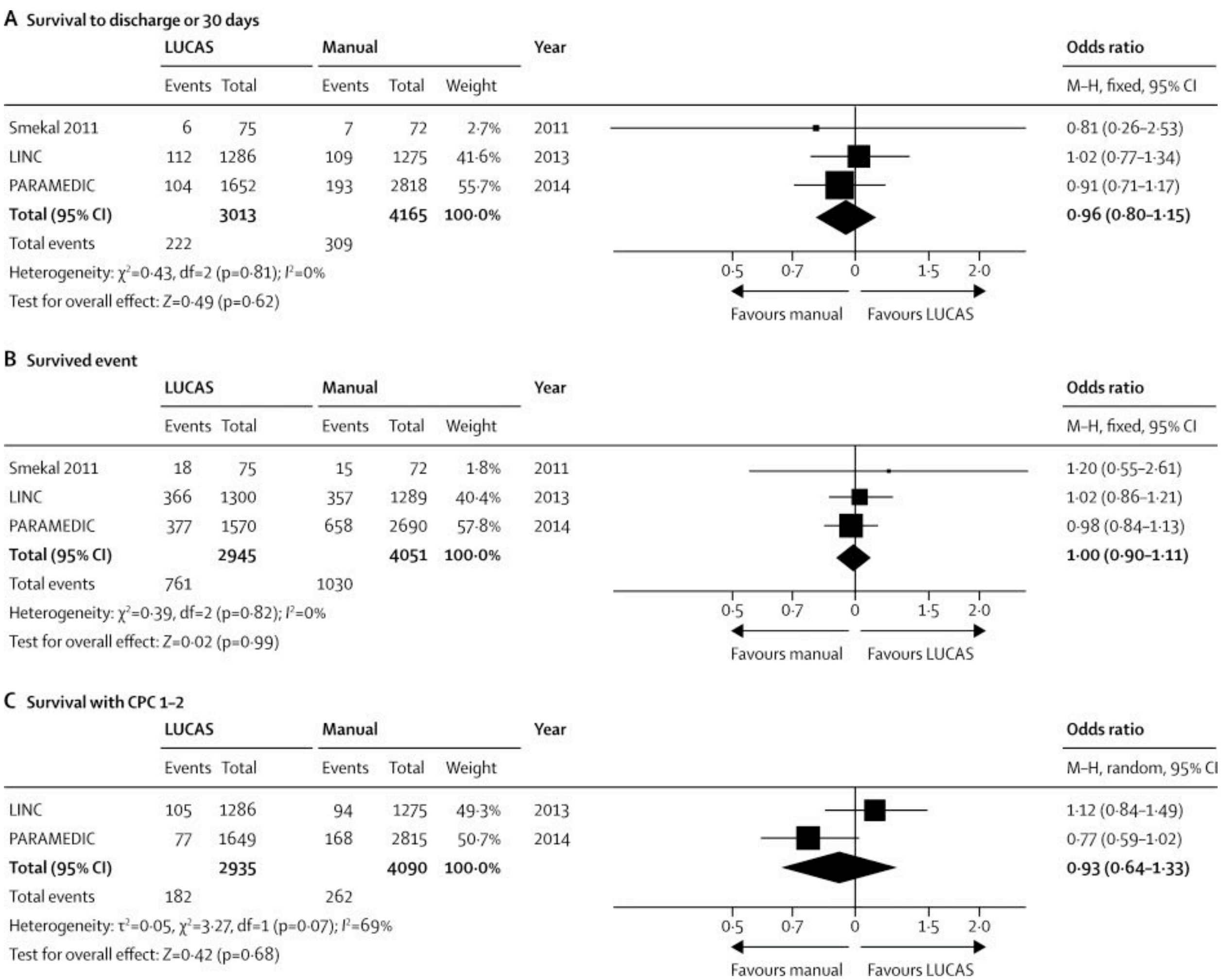

Fig. (1). Meta-analysis of the outcomes survived event and survival to hospital discharge or 30 days (**A**) Survival to discharge or 30 days. (**B**) Survived event. (**C**) Survival with CPC 1-2.
Reproduced with permission from Perkins *et al*. Mechanical *versus* manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): A pragmatic, cluster randomized controlled trial [24].

emergent surgery for cardiopulmonary bypass and lack of other supportive technologies [31]. Today ECPR is established by cannulating the femoral artery and vein to an external membrane oxygenator. There are no randomized trials comparing conventional CPR to ECPR however multiple observational studies and case series demonstrate the benefit of ECPR in refractory cardiac arrest patients. Multiple small studies showed the benefit of ECPR over conventional CPR in in-hospital refractory cardiac arrest patients [32-34]. The largest of these trials published by Chen *et al.* was a prospective observational study that included 113 patients enrolled in conventional CPR group and 59 patients in the ECPR group. After propensity matching there was a significant improvement in the survival to discharge rates, 30-day and 1 year survival rates in ECPR group [33]. The other common finding in all these studies was the timing of ECPR initiation, it was noted that survival to discharge was higher (50%) if ECMO was initiated within 30 minutes of cardiac arrest but decreasing to 30% when initiated between 30 and 60 minutes, and about 20% if its initiated past 60 minutes. These studies provide proof that ECPR can be a valuable tool in refractory in hospital cardiac arrest patients, provided it can be initiated within 30-60 minutes of arrest and the availability of trained personnel.

ECPR for OHCA refractory arrest patients present unique challenge in that for ECPR to be effective it has to be initiated "sooner than later". Needless to say, that the evidence for ECPR in OHCA is conflicting. A prospective observational study showed significant improvement in neurologically intact survival at 3 months in patients with OHCA who had ECPR compared to conventional CPR after propensity matching [34]. Another prospective observational study showed better neurological outcomes at 1 and 6 months in patients with OHCA who underwent ECPR combined with hypothermia and balloon pump compared to conventional therapy [35].

Another recent study showed favorable neurologically intact survival to discharge and at day 28 in patients with OHCA in whom ECPR was initiated within 20 minutes compared to delayed institution (> 30minutes) of ECPR [36]. The 2015 AHA guidelines on CPR gives a Class IIb- LOE C-LD for ECPR in select individuals for refractory cardiac arrest when it can be rapidly initiated and there is a potentially reversible cause for arrest [30].

7. THERAPEUTIC HYPOTHERMIA

Therapeutic hypothermia (TH) or targeted temperature management (TTM) is an established treatment strategy for a subset of patients with VF or pulseless VT cardiac arrest and post ROSC coma to improve neurological outcomes. Thus the 2015 guidelines on CPR issued a class I LOE B-R for TTM in these patients. The target temperature goal was however controversial but the guidelines offer a wide range between 32°C and 36°C [11]. The role of hypothermia in refractory cardiac arrest patients is not very clear. There are no randomized trials examining the role of TTM in these patients. However, there are multiple case reports and non-randomized observational studies that examined the role of hypothermia in combination with other invasive therapies such as ECPR and or early Coronary Angiogram (CAG) in refractory cardiac arrest patients [37-39]. Pang *et al.* examined the importance of TTM in refractory OHCA patients that received ECPR. This retrospective study showed a significant improvement in survival to discharge and good neurological outcome in patients who received ECPR and hypothermia [40].

8. EARLY CORONARY ANGIOGRAPHY

It is estimated that acute myocardial infarction (MI) accounts for 60% of all cardiac arrests [41]. It is clear from the 2015 guidelines that patients with OHCA and post resuscitation ECG showing ST segment elevation MI (STEMI) benefit from early CAG (Class I LOE B-NR) but its more controversial when there is no STEMI. The AHA guidelines do recommend early CAG for select comatose individuals (electrical or hemodynamic instability) in whom the OHCA is believed to be cardiac in origin even though the post resuscitation ECG do not demonstrate STEMI (Class IIa, LOE B-NR) [11]. A meta-analysis of 15 studies examined the importance of early CAG in survivors of OHCA and demonstrated a significant improvement in overall survival and survival with good neurological outcome in those patients who underwent early CAG. Of the 15 studies, 7 studies included patients without ST segment elevation on post resuscitation ECG and still demonstrated improvement in overall survival and survival with good neurological outcomes [42]. There are two contemporary trials that examined the importance of early CAG in combination to other invasive therapies in patients with refractory OHCA. Yannopoulos *et al.* published their experience with emergent angiogram with percutaneous coronary intervention (PCI), ECPR and mechanical CPR with LUCAS™ device in patients with refractory VF/VT arrest. Their protocol (University of Minnesota) for refractory VF/VT arrest included patients who continued to have VF/VT despite 3 shocks and IV amiodarone who then had LUCAS™ device placed and transferred directly to the cardiac cath lab (within 30 minutes) when emergent femoral arterial and venous access was achieved to place VA ECMO. Following this emergent angiogram, followed by PCI was performed as indicated. They reported 84% prevalence of coronary artery disease (> 70% stenosis) in these patients of whom 45% had significant three vessel CAD and 65% had acute thrombotic lesions. They demonstrated a significant improvement in survival with good neurological outcome in patients who had early CAG + ECPR + mechanical CPR compared to historical control [12].

CHEER trial was the second study that included patients with refractory cardiac arrest (in hospital and OHCA) defined as inability of achieve ROSC despite 30 minutes of CPR/ ACLS protocol and used an invasive treatment strategy that included mechanical CPR with AUTOPULSE™ device, emergent veno-arterial ECMO placement, intra-arrest cooling by IV infusion of cold saline and early angiography with PCI as indicated in these patients. This study showed a significant improvement in survival to hospital discharge with good neurological outcome in these patients in whom an invasive treatment strategy was used [43]. Both these studies underscore the importance of early angiography followed by PCI as indicated in this cohort of patients with refractory OHCA.

9. FUTURE DIRECTIONS

Despite significant improvements in drugs and invasive technologies, the survival rates remain poor in patients with refractory OHCA. The CPR community understands that there is no single treatment that is adequate to improve outcomes in these patients, rather there needs to be a correct combination of treatments that if employed in a timely fashion may result in improvement in survival to discharge rates with good neurological outcome. As mentioned above some of these trials that have already been published [12, 43] and others that are currently ongoing [39] will confirm the benefits of combination therapy. However, there are significant challenges and unanswered questions that remain in this area such as the definition of refractory OHCA, type of mechanical CPR device to use, why did the mechanical CPR devices not show superiority to conventional CPR, universal availability of ECMO device, challenges with infield ECMO placement, routine use of early coronary angiogram despite ECG not showing STEMI, pre-hospital therapeutic hypothermia and the need for dedicated cardiac arrest centers to treat these complex patients. Future trials should aim to clarify these questions in order to improve outcomes in patients with refractory OHCA.

CONCLUSION

Refractory OHCA is a common problem with poor overall survival and poor neurological outcomes. There has been a change in approach to these patients, rather than continuing repeated resuscitation attempts in the field, it is proposed to move these patients with mechanical CPR device in place to the closest hospital that is well equipped to care for these complex patients with advanced devices such as percutaneous ECMO placement, therapeutic hypothermia and early coronary angiography. However, the experience from some of the established programs that offer these treatments do clarify that it is critical to select patients who would most likely benefit from these therapies and also it is equally important to have trained personnel who can handle these patients. Refractory OHCA patients not only have poor overall survival rates, but also have poor neurological outcomes in those who make it to the hospital. Hence, aggressive post resuscitation care that includes hypothermia, prolonged hemodynamic support with ECMO or other devices and early CAG becomes critical in these patients.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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