CARDIAC ARREST MANAGEMENT REVIVED: AN INVASIVE PRE-HOSPITAL EXTENSION OF CPR

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Perspectives

It is probably among the most frightening sights to witness: somebody suddenly drops to the ground in agony and remains unresponsive. Annually, 6,200 people in the Netherlands are resuscitated with an acute cardiac arrest outside of the hospital, illustrating the magnitude of this problem [1]. Acute cardiac arrest predominantly occurs in men aged between 65 to 68 years [1]. In a best-case scenario, there are plenty of bystanders who are able to start resuscitation, an automatic external defibrillator (AED) is connected and the cardiac rhythm is shockable [1]. Efforts in the Netherlands expand to police and firemen serving as first responders and a call for trained civilians using a text message, resulting in relatively high survival rates [1]. Similarly, on international level attempts are made to improve survival. Lamhaut *et al*. recently took arrest management to the next level in Paris [2]. Additionally to standard resuscitation protocol, they used a device to temporarily support heart and lung function, in an out-of-hospital cardiac arrest setting [2].

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major cause of death in developed countries and affects approximately 360,000 people each year in the United States (US) alone [3]. OHCA is defined as an abrupt dysfunction of the cardiovascular system outside of the hospital caused by e.g. ventricular fibrillation, asystole or sustained ventricular tachycardia [3-4]. This, in turn, may be the result of a coronary syndrome. As a result of this dysfunction, vital organs do not receive sufficient blood supply [4]. The organs in the body cannot handle this insufficient organ perfusion for longer periods of time. Therefore, taking action aimed to quickly restore the circulation is essential in OHCA. Otherwise, the patient's death is inevitable. The current protocol for treating OHCA patients is to perform cardiopulmonary resuscitation (CPR) at the place of occurrence. Around the globe, CPR is widely accepted as the gold standard in regaining circulation in these patients. The current Dutch guideline, composed by the Dutch Resuscitation Council, defines the protocol for CPR as follows: when a person is found lying unresponsive and breathless, emergency services are called and resuscitation is started [5]. A cycle of thirty chest compressions and two artificial ventilations is repeated until there is a reason to stop the CPR [5]. The compressions should have a depth of around 5 to 6 cm and must be executed at a rate of 100 to 120 compressions per minute [5]. The time between the last and first compression (during artificial ventilation) should be as short as possible, with a maximum of ten seconds [5]. The impact of the chest compressions has been studied extensively, but there is less evidence regarding the additional value of the artificial ventilation [6]. Reasons to stop the CPR are return of spontaneous circulation (ROSC), the arrival of emergency medical services (EMS), exhaustion of the first-aid helper making it impossible to continue CPR or when a Do-Not-Resuscitate declaration is found [7]. The additional use of an AED has significantly increased the survival after CPR, although survival is still minimal [5]. Among people with a non-traumatic cardiac arrest treated by EMS, survival was 9.5% in 2010 in the US [8]. In 2018, this number increased to 10.8% [9]. In the Netherlands, survival in OHCA patients is reported notably higher, being 22.8% in 2016 [1].

Still, this shows the remaining potential to improve the survival of patients with OHCA. One upcoming intervention is the pre-hospital use of artificial oxygenation and perfusion support. In this article, we will first describe the technique in a hospital setting, then its novel use in a mobile outreach unit and finally evaluate the feasibility.

Artificial cardiopulmonary life support

As mentioned before, time is everything in case of an OHCA. If spontaneous circulation is restored on the scene, survival rates range between 20 to 50% [10]. This can be achieved by effective bystander CPR and the use of an AED. In case ROSC is not achieved, advanced life support (ALS; a professional extension of CPR) will be initiated by EMS, and continued in the hospital. Despite these efforts, cardiac arrest may persist which is commonly referred to as refractory OHCA if circulation is not restored within ten to thirty minutes [11]. In this dire event, ALS will often be ceased as patients seem to have practically no chance of survival with acceptable clinical outcome [11]. However, techniques have been developed to mechanically maintain an effective circulation until spontaneous circulation is restored.

Extracorporeal (i.e. outside of the body) membrane oxygenation (ECMO) is a cardiopulmonary life support method [12]. A pump drains blood from the vascular system, which is oxygenated outside the body, and then reinfused. ECMO has many clinical indications in which the cardiac or pulmonary system fails. It is mostly used in neonatal and pediatric care but can be deployed for resuscitation purposes (ECPR) [12]. According to the clinical situation, different techniques can be used to support the patient. If only respiratory support is needed, ECMO is connected to two veins and will form a circuit in series with the heart [12]. In case of ECPR, the ECMO will have to support the circulation as well. It will receive oxygen deprived blood from the femoral vein and reinfuses oxygenated blood in the contralateral femoral artery, bypassing the heart and lungs [2, 12, 13]. The femoral vessels are preferred because of their readily accessible location (as shown in figure 1) [12]. While supported by ECMO, patients may receive necessary treatment such as heart catheterisation, a coronary bypass or thrombolysis [11]. After successful therapy, patients can be gradually weaned (i.e. detached) from ECMO after a median duration of two days, which can range between one to five days [13]. Ortega-Deballon *et al.* recently reported the overall survival rate of ECPR in OHCA in a systematic review of international literature. The overall survival rate of ECPR was twenty-two percent of which approximately sixty percent with good neurological recovery, opposed to two percent to elevent percent survival with standard care [11]. ECPR seems a feasible in-hospital strategy in patients who would otherwise have almost no chance of survival. Still, randomised controlled trials are currently performed to confirm these results and further clarify patient selection

Pre-hospital ECMO

Positive outcomes of ECPR seem to be more pronounced if there is a short delay in its initiation [2, 14]. Accordingly, the pre-hospital use of ECMO was proposed to further reduce delay [15]. In 2013, Lamhaut *et al.* published a pilot study showing the feasibility and safety of a pre-hospital ECPR protocol, after which they completed a large observational study in Paris until 2015 [2, 15]. During this period, a pre-hospital ECPR team was dispatched in a mobile intensive care unit if an OHCA patient met inclusion criteria (signs of life and electric heart activity amongst others) and if transportation time to the hospital was estimated to be more than ten to twenty minutes [2]. Patients with lower estimated transportation time and a cardiac arrest during transportation were allocated to in the in-hospital group. An emergency physician or intensivist coordinated the team, further consisting of a nurse anaesthetist and a paramedic. Mechanical CPR was continued until the ECMO was connected [2]. Their efforts shortened the duration in which the patients were in a state of low blood flow (i.e bystander -and mechanical CPR), and lowered the time to ROSC significantly [2]. After optimising their protocol, survival was 38% in a select group of pre-hospital ECPR patients, suggesting good potential for its implementation [2]. However, with propensity score matching (a statistical method to filter out other factors that could have explained the results i.e. reducing confounding) pre-hospital ECPR was not significantly different from in-hospital ECPR [2].

Future Perspectives

There are limitations to the aforementioned studies examining the use of the pre-hospital ECPR. The reduction in low-flow duration was not accompanied by increased survival in the pre-hospital group [2]. This is in conflict with the inverse relationship between survival and low-flow duration described by Chen *et al.* [14]. Lamhaut *et al.* suggests this lack of difference could be due to selection bias towards in-hospital ECPR in their study. Some patients with in-hospital ECPR were excluded after losing their inclusion criteria by losing signs of life or electric heart activity during transportation [2]. Accordingly, less severe arrhythmias seemed to remain included in the in-hospital group, possibly leading to similar survival rates of the pre-hospital group.

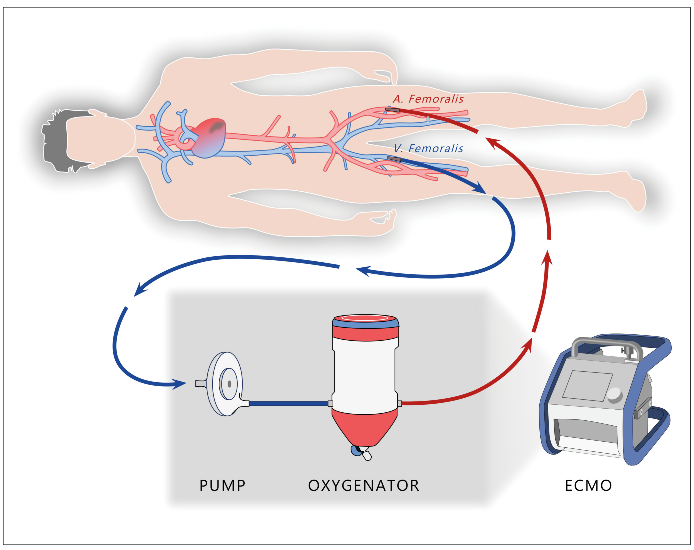

Figure 1: Schematic overview of extracorporeal membrane oxygenation (ECMO)
Oxygen deprived blood is taken from the femoral vein (blue arrow) and is driven through the pump. Next, it is oxygenated inside the device, and subsequently reinfused in the contralateral femoral artery (red arrow) [12]. Hereby, the ECMO bypasses the heart and lungs and supports both hemodynamics and oxygenation.

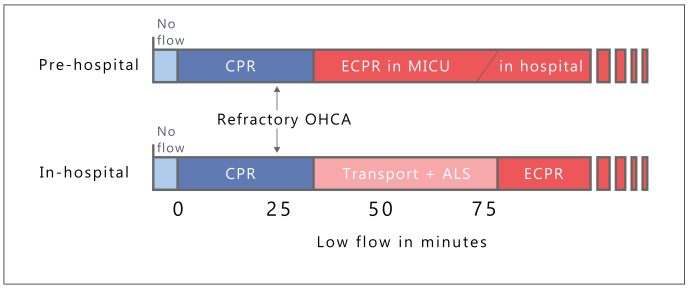

Figure 2: Comparison of the management strategy of low flow for out-of-hospital cardiac arrest (OHCA) between pre-hospital and in-hospital extracorporeal cardiopulmonary resuscitation (EPCR).
In pre-hospital ECPR, patients are connected to ECPR in the mobile intensive care unit (MICU), whereas patients undergo advanced life support (ALS) during transport in the in-hospital ECPR.

Furthermore, the pre-hospital ECMO has only been tested and used in Paris, so it remains to be seen whether it will function in other places as well. In the US for example, the termination of resuscitation (TOR) is in use. TOR states that after at least four two-minute intervals of CPR resuscitation attempts should be terminated if: 1) arrest was not witnessed by EMS, 2) there is no shockable rhythm and 3) no ROSC [16]. The existence of this rule hinders the implementation of pre-hospital ECPR because pre-hospital ECPR is often started without the presence of ROSC and TOR allows transportation only when ROSC is present.

In the Netherlands, little experience with in-hospital ECPR is present, as only a few hospitals have got an ECPR team (including Rotterdam, Nijmegen, The Hague and Leiden). Of these centres, only two are so-called 'centres of excellence' awarded by the Extracorporeal Life Support Organisation (ELSO) [17]. These centres are recognised by the ELSO as centres which have been present for a few years and treated at least five patients a year during at least five years [18]. The other centres do not fulfill these criteria and are thus not experienced enough. Due to this lack of experience, the implementation of pre-hospital ECPR might be a challenge. Generally, the Netherlands is less crowded than Paris, so transportation to a hospital takes less time. According to the Dutch Heart Association this takes approximately eight minutes [1]. As low-flow duration remains fairly short this way, pre-hospital ECPR might not be of additional benefit in the Netherlands. Importantly, costs related to the logistics to be able to perform ECPR, in-hospital and pre-hospital, will be extensive. As survival in the Netherlands is relatively high, limited improvements to survival can be expected. Therefore, the costs might outweigh the benefits of the pre-hospital ECPR. At this moment, a randomised comparative study by Lamhaut *et al.* is running in France. This study aims to answer whether pre-hospital ECPR is more favourable than in-hospital ECPR [19]. Until now, no randomised study has been performed into this topic.

Conclusion

The ultimate goal is to improve survival in patients with refractory OHCA, which requires new techniques and strategies. At this point, survival is low, with only 22.8% in the Netherlands and 10.8% in the US. In Paris, pre-hospital ECPR is used as a novel treatment for refractory OHCA. The effectiveness of this technique is poorly studied, but recent literature hints towards the potential of this strategy to improve survival by significantly reducing the low-flow duration. However, limitations are evident in these studies, so more research is necessary to further determine the feasibility and therapeutic efficacy of this treatment. The first steps are made as, at the moment, a study in Paris investigates whether pre-hospital ECPR is worthwhile or not.

Acknowledgements

RAMS would like to thank prof. dr. R.P. Pickkers, specialist internal-medicine in the Radboud university medical center, Nijmegen, the Netherlands with expertise in experimental intensive care medicine, for providing the authors with insights into the subject and feedback on this article.

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CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1:
B. ATP

The breakdown of one mol of C16 fatty acids (palmitate) leads to a gross total yield of 108 mol of ATP. Via oxidation of acetyl-CoA by the citric acid cycle, 80 mol of ATP is synthesised, while 28 mol of ATP is released with the conversion of NADH and FADH2 due to β-oxidation. When it is taken into account that two high-energy phosphates are necessary for the initial activation step, the net gain per mol of palmitate is 106 mol ATP (3233 kJ), which represents 33% of the free energy of combustion of palmitic acid.

For further reading:
Botham, K.M., *et al. Oxidation of Fatty Acids: Ketogenesis*. in Harper's Illustrated Biochemistry, Vol. 31e. (McGraw-Hill Education, New York, NY, 2018)

During the exam, 60% of the participants answered this question correctly.

Answer question 2:
C. A QRS-width > 0.12 s. with a positive 'notched' QRS in lead V6

In a left bundle branch block, the left ventricle activation is delayed. This causes the ventricles to contract slower, which results in a positive notched V6. In a left bundle branch block, a deep S wave in lead V1 and a tall late R wave in leads I and V6 can be seen on the ECG. The left bundle branch is also responsible for the initial ventricular activation, which leads also to abnormal Q waves when there is a left bundle branch block.

For further reading:
Bunce, N.H. and Ray, R. *Cardiovascular Disease* - Heart Block in Kumar and Clark's Clinical Medicine, Vol. 9e (Elsevier Ltd, the Netherlands, 2017)

During the exam, 46% of the participants answered this question correctly.

The exam questions can be found back on page 6 in this journal.

Assembly of the clinical issues (KVS) exam

The KVS exam is assembled by the KVS-committee, where many medical specialties are represented. This committee gathers once every two weeks, and during these meetings, new questions (provided by all module coordinators) are evaluated in their appropriateness for the exam. After the exam is made by students, this committee looks extensively to the exam analysis and comments of the students. From this evaluation, it is decided what happens with these questions. Recently, the committee decided that a reaction to the student's commentary will be made available to read for all students. The final grading is then determined based on the Cohen-Schotanus formula, after which the final grades will be checked again and made public within 15 working days after the exam date.