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Journal of Cardiovascular Emergencies 2016;2(4):151-158
DOI: 10.1515/jce-2016-0029

REVIEW

New Developments in the Treatment of Acute Myocardial Infarction Associated with Out-of-Hospital Cardiac Arrest. A Review

Monica Marton-Popovici[1], Dietmar Glogar[2]

[1] Swedish Medical Center, Department of Internal Medicine and Critical Care, Edmonds, Washington, USA
[2] Medical University of Vienna, Austria

ABSTRACT

Out-of-hospital cardiac arrest (OHCA) occurring as the first manifestation of an acute myocardial infarction is associated with very high mortality rates. As in comatose patients the etiology of cardiac arrest may be unclear, especially in cases without ST-segment elevation on the surface electrocardiogram, the decision to perform or not to perform urgent coronary angiography can have a significant impact on the prognosis of these patients. This review summarises the current knowledge and recommendations for treating patients with acute myocardial infarction presenting with OHCA. New therapeutic measures for the post-resuscitation phase are presented, such as hypothermia or extracardiac life support, together with strategies aiming to restore the coronary flow in the resuscitation phase using intra-arrest percutaneous revascularization performed during resuscitation. The role of regional networks in providing rapid access to the hospital facilities and to a catheterization laboratory for these critical cardiovascular emergencies is described.

Keywords: out-of-hospital cardiac arrest, cardiopulmonary resuscitation, life support, intra-arrest PCI

ARTICLE HISTORY

Received: 16 September, 2016
Accepted: 10 November, 2016

CORRESPONDENCE

Monica Marton-Popovici
Swedish Medical Center
Department of Internal Medicine and Critical Care
21601, 76th Ave W, Edmonds,
Washington, 98026, USA
E-mail: monica.marton-popovici@swedish.org

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) occurring as the first manifestation of an acute myocardial infarction (AMI) is associated with very high mortality rates. When cardiac arrest occurs out-of-hospital, delays in the initiation of resuscitation can lead to a poorer prognosis and a significant neurological deficit, even in the eventuality of a successful resuscitation. As in many circumstances the etiology of cardiac arrest remains unclear in comatose patients, especially in those cases without ST-segment elevation on the surface electrocardiogram, the decision to perform or not to perform urgent coronary angiography can have a crucial impact on the prognosis of these patients. New therapeutic measures such as hypothermia and extracardiac life support have been proposed to improve survival rates in these critical cardiac emergencies. Intra-arrest percutaneous coronary intervention (PCI) has also been attempted in the hope that urgent revascularization of the occluded coronary artery may lead to the immediate restoration of myocardial contractility and recovery of the circulation (Figure 1). This review summarizes current knowledge and recom-

Dietmar Glogar: Medizinische Universität Wien Univ. Klinik für Innere Medizin II Abteilung für Kardiologie Waehringer Guertel 18-20, A-1090 Wien, Austria.
E-mail: d.glogar@aon.at

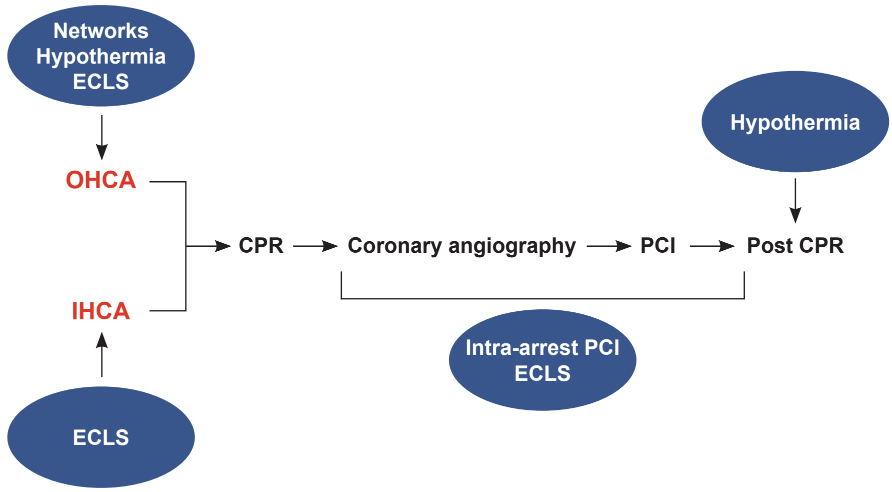

FIGURE 1. Modern approaches in cardiac arrest with suspected ischemic etiology.

OHCA – out-of-hospital cardiac arrest, IHCA – in-hospital cardiac arrest, ECLS – extra-corporeal life support, CPR – cardiopulmonary resuscitation, PCI – percutaneous coronary intervention

mendations for treating patients with AMI presenting with OHCA.

OUT-OF-HOSPITAL CARDIAC ARREST — A MAJOR HEALTHCARE PROBLEM

Out-of-hospital cardiac arrest (OHCA) is defined as an unexpected sudden onset condition with the absence of palpable central pulse and apnea, attributed to mechanical cardiac inactivity. Although the incidence and survival rates associated with this condition vary considerably in different regions of the world, it remains one of the leading causes of death and invalidity in industrialized countries, with a summary incidence of 38 per 100,000 person-years for all-rhythm OHCA in Europe.[1,2] The main etiologies of OHCA are represented by different cardiovascular conditions, mainly attributed to ischemic heart diseases complicated by an acute coronary syndrome (ACS) or a stroke.[3] However, it was reported that between 20% and 40% of OHCA in adult patients were of non-cardiac origin, indicating that further investigations are needed to identify other risk factors involved in OHCA etiology.[4] Survival rates of OHCA patients also show considerable variability for different countries and regions depending on the standard of medical education about cardiopulmonary resuscitation (CPR), on the development of emergency medical services (EMS) and on public access to external defibrillators.[5] In developing countries, the incidence of cardiovascular diseases and OHCA is higher than in industrialized countries. The lack of standardized emergency medical systems and poor public awareness predisposes to mortality rates as high as 98–100% in these regions.[6] In one study it was suggested that the survival rate of OHCA patients might be age- and sex-related, with a higher overall rate of survival in women, with differences across age groups, indicating that women younger than forty-seven years had a higher probability of survival after an OHCA.[7]

OUT-OF-HOSPITAL CARDIAC ARREST ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION

Despite the progress made in the last decades in the prevention of coronary artery diseases (CAD) and improved treatment strategies with either optimal medical therapy or percutaneous coronary interventions (PCI) for ischemic heart diseases, the mortality associated with acute myocardial infarction (AMI) is still high.[8–10] A substantial number of sudden cardiac arrests related to AMI occur outside the hospital, and this is associated with higher mortality rates compared to patients with in-hospital cardiac arrest (IHCA). This is mainly attributed to the late initiation of CPR and advanced life support therapies in out-of-hospital settings.[11] A significant number of OHCA survivors have a low quality of life due to significant neurological sequelae secondary to cerebral hypoxia.[12] Ostenfeld *et al.* (2015) evaluated mortality in patients with AMI complicated by cardiogenic shock (CS) presenting with or without OHCA and found no significant differences in survival rates between the two groups, suggesting that OHCA cannot be considered as an independent predictor of mortality in the severe group of AMI patients with CS.[13]

MANAGEMENT OF PATIENTS SURVIVING OHCA

RECOMMENDATIONS FOR REVASCULARIZATION IN OHCA ASSOCIATED WITH AMI

As multiple non-randomized trials suggest that OHCA survivors can benefit from immediate coronary angiography and PCI, with improved survival rates following revascularization procedures, the guidelines of the European Society of Cardiology (ESC) recommend emergency coronary angiography with revascularization in patients with AMI and OHCA, regardless of ECG findings, as a class IIa indication. According to ESC guidelines, conscious patients surviving OHCA with ST-segment elevation myocardial infarction (STEMI) should be treated immediately with PCI, while high-risk non-ST-segment elevation acute coronary syndrome should receive rapid invasive therapy in less than two hours.[14] Unconscious patients should be transferred immediately to the catheterization laboratory.[15] The guidelines of the American Heart Association (AHA) recommend emergency coronary angiography and PCI for the management of OHCA patients if the ECG shows STEMI (Class I, level of evidence B) and emergency angiography of comatose patients regardless of ST-segment elevation on the ECG (Class IIa, level of evidence B).[16]

CORONARY ANGIOGRAPHY AND REVASCULARIZATION IN OHCA PATIENTS

The majority of OHCA events associated with AMI result from erosion or rupture of an atherosclerotic coronary plaque,[17] and numerous studies suggest that to decrease mortality, conventional immediate angiography and revascularization should be performed for survivors of OHCA, regardless of ECG changes and symptoms.[18] Waldo *et al*. (2015) proposed a straightforward and easily measurable score based on four risk variables in resuscitated patients, including angina, congestive heart failure, the presence of a shockable rhythm on an electrocardiogram as the initial rhythm, and ST-segment elevation in at least two contiguous leads. Patients with a risk score ≤1 are considered as a slight risk of having an acute culprit lesion. Thus, they should not be referred for immediate coronary angiography. A risk score >1 is associated with a high likelihood of having an acute coronary lesion, and these patients may benefit from invasive coronary angiography. However, further prospective studies are needed to validate this clinical risk model.[19]

The importance of early coronary angiography for cardiac arrest survivors is augmented by recently published results. Kern *et al*. (2011) demonstrated better outcomes regarding survival and neurological function for patients receiving immediate coronary angiography, regardless of ST-segment changes. A recent study on OHCA patients undergoing urgent catheterization indicated that coronary angiography revealed an acute coronary occlusion in one out of four patients with OHCA without STEMI.

Patients with ST-segment elevation or left bundle branch block (LBBB) with the return of spontaneous circulation (ROSC) following resuscitation, are also likely to benefit from early invasive management and should be referred immediately to the catheterization laboratory. Observational studies demonstrated better outcomes, with reduction of in-hospital mortality and higher rate of a favourable neurological status, when early PCI was associated with targeted temperature management.[22–25]

In patients without ST-segment elevation, as recorded on the post-ROSC electrocardiogram, the decision to perform early PCI can depend on numerous factors.[26] As the specificity and sensitivity of clinical data and biomarkers are less accurate after OHCA, a decision may be extremely difficult to arrive at in such cases. Hemodynamic status, age, duration of CPR or neurological status can all influence the decision of undertaking or postponing coronary angiography. The current consensus released by the European Association for Percutaneous Cardiovascular Interventions (EAPCI) stated that where there is of lack of an apparent non-coronary cause of OHCA, coronary angiography should be performed in less than two hours.[24,25,27]

A recent study that included 407,974 patients with OHCA presenting with ventricular tachycardia or ventricular fibrillation as initial rhythm, discussed the current trends, outcomes and predictors of performing coronary angiography and PCI in this group. Coronary angiography was performed in only 35% of patients, increasing from 27.2% in 2000 to 43.9% in 2012, while the PCI rate increased from 9.5% to 24.1% during this period. The overall survival-to-discharge rate increased from 46.9% to 60.1% ($p < 0.001$ for trend) in the overall study population, with an increase from 59.2% to 74.3% ($p < 0.001$ for trend) in patients with STEMI and from 43.3% to 56.8% in those without ST-segment elevation. The study concluded that even if survival-to-discharge rates have increased, a significant number of OHCA patients are still not investigated using coronary angiography.[28]

Geri *et al*. (2015) analyzed the short- and long-term mortality of patients who underwent immediate coronary angiography and PCI after OHCA. In this study 1,722 patients were included, 628 (35.6%) receiving coronary angiography, 615 (35.7%) receiving coronary angiography without PCI and 479 (27.8%) receiving PCI. Thirty-day survival rates were 21%, 11.9% and 35% respectively and the ten-year survival rates were 29%, 43% and 38% respectively in this patient population. Patients with immediate PCI after OHCA presented a significantly lower risk of mortality in the long-term. This study demonstrated that PCI should be carried out in all OHCA survival patients with no obvious non-cardiac cause for the cardiac arrest.[29,30]

Another study which analyzed the short- and long-term outcomes of emergency coronary angiography after OHCA in comatose patients with STEMI or non-STEMI, revealed that age, time to ROSC and the presence of co-morbidities were independent predictors of thirty-day and one-year mortality in STEMI patients, while no clinical benefit of immediate coronary angiography/PCI was identified in patients without STEMI.[31]

INTRA-ARREST PCI — A VALID CONCEPT?

Even though early revascularization therapy is recommended for cardiac arrest survivors, only a few studies addressed the role and clinical benefits of intra-arrest PCI.[32] In an observational study Kagawa *et al*. (2012) included 86 patients with ACS unresponsive to conventional CPR. Intra-arrest PCI combined with rapid-response extracorporeal membrane oxygenation (ECMO) was performed for 61 patients (71%), leading to return of spontaneous heartbeat in all cases. Mild hypothermia was induced in thirty-two patients (37%) in this study. In patients who survived up to thirty days, the rate of OHCA was lower (28% vs. 58%; $p = 0.01$), the time interval from the arrest to the initiation of extracorporeal life support was shorter (40 minutes vs. 54 minutes; $p = 0.002$) and the rate of intra-arrest PCI was higher (88% vs. 70%; $p = 0.04$). At the same time, the thirty-day survival rate was greater in patients with intra-arrest PCI (36% vs. 12%; $p = 0.03$). The study concluded that intra-arrest PCI combined with extracorporeal life support was associated with better survival rates for patients with refractory cardiac arrest, demonstrating that intra-arrest PCI is a valid concept that requires further development.[33]

POST-RESUSCITATION CARE – THERAPEUTIC HYPOTHERMIA AFTER OHCA

Induced mild hypothermia after global cerebral hypoxia is associated with improved outcomes as a consequence of the neuroprotective effect, via suppressing different pathways of cell death, decreasing cerebral oxygen consumption and reducing the release of stimulatory amino acids and free radicals.[34–37]

Over the last decade, therapeutic hypothermia has become standard care for comatose patients after OHCA with a shockable rhythm, but an analysis of the current studies on therapeutic hypothermia in patients with non-shockable rhythm indicates that controversy still exists.

A large cohort study compared mild induced therapeutic hypothermia at 32–34°C for 24 hours, followed by passive 0.3°C per hour rewarming to 37°C in 24 hours with no temperature management in patients after OHCA. This study demonstrated a better neurologic outcome at discharge for patients with initial VT/VF rhythm compared to those in pulseless electrical activity (PEA)/asystole (39% vs. 16%; $p < 0.001$).[38,39] Testori *et al*. (2011) investigated the outcomes of patients with non-shockable initial rhythm after OHCA treated with mild induced therapeutic hypothermia for 24 hours, and demonstrated improved neurological outcome at discharge, associated with a reduced risk of mortality.[40,41] The FINNRESUSCI study (2013) also reported improved neurological status at one-year follow-up in patients with shockable rhythm after OHCA with therapeutic hypothermia, but no benefit was observed for patients with non-shockable rhythm.[42]

In the Targeted temperature management (TTM) trial (2013), 950 unconscious OHCA patients were randomly assigned to TTM at either 33°C or 36°C, achieved as rapidly as possible with ice-cold fluids and ice packs. After twenty-eight hours re-warming to 37°C was performed in both groups. No significant differences were observed in the primary outcome of all-cause mortality at the end of the trial between the two groups. The six-month neurological outcome was also similar in the two groups.[43,44]

An extensive retrospective registry study, which compared the effectiveness of therapeutic hypothermia after OHCA, found no significant neurological benefit at discharge compared to no temperature management, reporting worse neurological outcome in patients with non-shockable rhythm.[45,46]

The optimal duration of TTM is yet unknown, but currently, most recommendations indicate that this therapy should be maintained for at least twenty-four hours. No differences were observed in mortality and neurological outcomes with twenty-four-hour versus seventy-two-hour hypothermia. Current European Resuscitation Council and European Society of Intensive Care Medicine guidelines recommend that a target temperature between 32–36°C should be achieved if TTM is used after OHCA. According to these guidelines, TTM is recommended after

OHCA for patients with shockable rhythm on initial ECG, who are unresponsive after ROSC, and for those with initial non-shockable rhythm on the ECG who remain unresponsive after ROSC. According to current recommendations, TTM should be maintained for at least twenty-four hours.[47] ESC and AHA guidelines also recommend (Class I indication) the use of TTM for STEMI patients who are resuscitated after cardiac arrest but remain comatose at arrival at a hospital.[48,49]

The duration of coma in OHCA survivors is related to various factors, such as the duration of cardiopulmonary resuscitation, initial rhythm, arrest location, witnessed arrest, and sex. In an observational study on 573 patients with OHCA treated with TTM, 316 patients (55%) became responsive, 60 (19%) woke up at least 48 hours after re-warming and 8 patients (2.5%) woke up more than one week after re-warming. This study also observed a better neurological status at discharge in early awakeners.[50]

As the use of TTM becomes more frequent in clinical practice, safety issues arise in relation to this new strategy. Bleeding, infectious and arrhythmic complications have been reported. TTM can alter the coagulation cascade, and dual antiplatelet therapy combined with potent antithrombotic agents can increase bleeding risk for patients undergoing PCI. A meta-analysis of five studies reported no significant increase in bleeding complications or blood transfusion for patients with TTM treatment.[51] Joffre *et al.* (2014) reported a higher rate of stent thrombosis in comatose patients with OHCA treated with TTM and PCI. This could be explained by the pharmacokinetic changes following hypothermia, the higher rate of nonresponders to clopidogrel, the presence of circulatory shock or insufficient antiplatelet therapy.[52] Another study, which evaluated the incidence of stent thrombosis in 49,109 patients treated with TTM and PCI for AMI after cardiac arrest, concluded that the rate of stent thrombosis was not significantly different in patients who received TTM compared to those on standard care.[53,54]

In a systematic review on therapeutic hypothermia after cardiac arrest, it was reported that excellent survival rates with clear neuroprotective benefit followed the use of therapeutic hypothermia (TH), regardless of initial rhythm after survival of OHCA. However, this study did not demonstrate any evidence in favour of a specific temperature.[55,56]

The timing of initiation of TH is still a topic of debate. Some authors suggest that early initiation of TTM, with prehospital initiation, could be beneficial for OHCA patients, preventing profound brain injury and limiting early reperfusion injury. As yet no clinical benefit has been proven for this approach, which was also associated with longer times from therapy initiation to hospital arrival.[57–59]

POST-RESUSCITATION SUPPORTIVE THERAPY IN OHCA PATIENTS

Extracorporeal life support (ECLS) is a secondary therapy to conventional CPR, which is associated with improved survival and neurological outcomes. It is mainly used if there is a suspected reversible etiology related to the cardiac arrest. ECLS can be initiated at the site where OHCA occurred. However, the results were significantly worse in OHCA than in-hospital cardiac arrest (IHCA).[60–63] A recent meta-analysis on the efficacy of extracorporeal cardiopulmonary resuscitation compared to conventional CPR revealed no differences in survival rates and neurologic outcomes in OHCA patients, despite this therapy leading to improved survival and better neurologic outcome in IHCA of cardiac origin.[64]

Another approach, which raises serious ethical questions, is the use of extracorporeal membrane oxygenation (ECMO) to preserve organs for transplantation from refractory OHCA patients.[65] Dalle *et al.* (2016) suggested that ECMO should be used for ECPR, as well as for uncontrolled donation after circulatory determination of death for organ transplant-eligible patients. However, only top centers in ECLS should develop this kind of protocol, and ECLS should always be considered before the initiation of these protocols.[66,67]

NETWORK DEVELOPMENT FOR REDUCTION OF MORTALITY

The most frequent underlying cause of OHCA is the presence of an ACS, and emergency PCI may be associated with improved survival in these cases.[23,68] The development of well-organized STEMI networks has led to a significant reduction of in-hospital mortality in STEMI patients, and OHCA patients may also benefit from these networks.[69–71] The development of highly specialized centers for cardiac arrest, with well-trained staff and state-of-the-art equipment, capable of primary PCI and advanced post-resuscitation care, can also have a role in reducing mortality and achieving better neurological outcomes.[72–76] A system-wide approach for early CPR in the community could also achieve decreased death rates for OHCA patients and improve neurological outcomes.[77–79] The implementation and development of OHCA registries may lead to a better understanding of these complex conditions and help identify the needs for targeted interventions in regional networks.[80,81]

CONCLUSIONS

Acute myocardial infarction associated with cardiac arrest remains a major healthcare problem, and OHCA occurring at the onset of infarction requires prompt intervention to identify the ischemic cardiac etiology of the cardiac arrest accurately and to initiate appropriate reperfusion strategy. Urgent coronary angiography should be performed in all cases with suspected ischemic etiology and in all cases with unknown etiology of the cardiac arrest, as revascularization of the culprit lesion has been demonstrated to improve the survival in these patients. Complex therapeutic strategies have been proposed to reduce the mortality associated with this condition. However, few strategies have been linked with a significant decrease in mortality. The implementation of modern approaches in the therapeutic algorithm dedicated to OHCA still requires significant efforts and the organization of efficient regional networks for acute cardiac care.

CONFLICT OF INTEREST

Nothing to declare.

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