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ARTICLE

Post-Resuscitation Care: the Role of Early Percutaneous Coronary Intervention

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LIST OF ABBREVIATIONS:
AMI = acute myocardial infarction
CA = cardiac arrest
CPR = cardiopulmonary resuscitation
PCI = percutaneous coronary intervention
OOHCA = out-of-hospital cardiac arrest
IHCA = in-hospital cardiac arrest
ROSC = return of spontaneous circulation
STEMI = ST-segment elevation myocardial infarction
TIMI = thrombolysis in myocardial infarction
CPC = cerebral performance category

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ABSTRACT

BACKGROUND: The outcome of resuscitated cardiac arrest (CA) patients remains poor, despite current advances in cardiopulmonary resuscitation (CPR). Although the majority of cases are of cardiac origin, the decision to perform percutaneous coronary intervention (PCI) is challenging due to the lack of randomized trials and the uncertainty of the neurological outcome. We sought to review the current evidence of early PCI in patients resuscitated after CA with regard to its feasibility, success and long - term outcome.

METHODS AND RESULTS: The studies for our review were identified from PubMed and references from relevant studies and review papers. We included 19 studies between 1997 to 2010, reporting on adult survivors of cardiac arrest who underwent PCI. The survival at discharge varied from 38% to 80%, with 34% to 71% of patients having a favorable neurological outcome. Main independent predictors of survival were the time interval between CA and the start of CPR, the existence of a shockable rhythm, early defibrillation, absence of cardiogenic shock, neurological status on admission, and the implementation of PCI. In some studies, significant coronary lesions amenable to PCI were also found in cardiac arrest patients without evidence of pre-arrest myocardial infarction. As there is no sensitive marker regarding neurological prognosis and many comatose patients regained full neurological function at follow up, several authors suggest that there should be a low threshold for urgent PCI, even in patients with depressed sensorium.

CONCLUSION: PCI improves survival in CA patients with ST-elevation myocardial infarction, and should also be considered in survivors of cardiac arrest of presumed cardiac origin, even in cases with poor neurological status on admission. The role of PCI, its long term effectiveness and feasibility at an organizational level need further research.

INTRODUCTION

Each year approximately 700,000 cases of cardiac arrest occur in Europe,[1] mostly due to cardiac causes. Spaulding et al performed immediate coronary angiography and angioplasty (when indicated) in survivors of out-of-hospital cardiac arrest (OOHCA). Sixty of 84 patients had clinically significant coronary artery disease on

angiography, and 40 of them had coronary-artery occlusion (48%).[2] In accordance with these data, Davies et al studied the pathology of the myocardium and coronary arteries in ambulatory subjects dying suddenly of coronary heart disease; in 168 consecutive cases of sudden coronary death, 73.3% had a recent coronary thrombotic lesion.[3] Authors suggested that acute thrombosis and subsequent ischemia comprised the pathophysiological substrate that led to arrhythmias and subsequently to cardiac arrest. Nowadays patients with ST-segment elevation myocardial infarction (STEMI) are treated with an aggressive revascularization strategy, resulting in high success and survival rates. Unfortunately for patients who survived an OOHCA the existing data are not satisfying, as in most studies they were excluded according to selection criteria.

Patients who survived a cardiac arrest are a special group of patients with special diagnostic and therapeutic dilemmas. In particular, the interpretation of post resuscitation ECG often presents difficulties, as its sensitivity and specificity varies across different studies.[2,4,5] Furthermore, the efficacy of thrombolysis after cardiac arrest (CA) is still debated,[6,7] and even if we adopted an expensive and advanced medical approach, as the mechanical reperfusion therapy (PCI), the benefit would not surpass the expected severe permanent brain disability.

METHODS

DATA SOURCES – STUDY SELECTION

The studies for our review were identified from PubMed (until June 2010) and references from relevant studies and review papers. Search terms included: "sudden cardiac death", "cardiac arrest", "primary angioplasty", and combinations of these terms. Two independent reviewers did literature searches and examined the identified relevant studies for further evaluation of data. A study was eligible for inclusion in the review if it assessed the role of early PCI in cardiac arrest patients.

RESULTS & DISCUSSION

URGENT PCI IN RESUSCITATED PATIENTS WITH STEMI

Kahn et al selected 11 patients from a prospective database which included all emergency group admissions following OOHCA during 5 years. They were the first to report a group of patients who survived from cardiac arrest after STEMI and immediately transferred to the catheterization laboratory for angiography and subsequent primary angioplasty (PCI) of the infarct related artery (Table 1). Although the number of patients in this study, is relatively small, authors concluded that urgent PCI is feasible and beneficial, even in patients with depressed sensorium.[8]

Several studies followed, with small numbers of patients (Table 1). Inclusion criteria consisted of ST elevation, or presumed new left bundle branch block (LBBB) in survivors of cardiac arrest. Data in these studies were heterogeneous and they did not share the same endpoints. Some of them included OOHCA and others in hospital cardiac arrests (IHCA), and each of them monitored different parameters, hemodynamic or neurological. Epidemiological and angiography data vary, although it seems that ventricular tachycardias are more often encountered than asystole.[2,5,9-12]

Anterior STEMI occurred most frequently (43.2% to 67%),[8,10-16] and the affected artery was the left coronary artery and in particular the left anterior descending.[8,9,11-13,16,19-22] Door to balloon time, when reported, was consistent with the STEMI guidelines and did not exceed 190 min.[9,11,12,14,15,17,19,21,23,24] (Table 1). All patients received conventional antithrombotic treatment, and in more recent studies patients received intravenous antiplatelet agents,[9-12,14,17,21] while there was variable utilization of hypothermia.[5,11,12,14,17,20-22] In all studies the percentage of successful angioplasty, as it is represented by TIMI 3 flow (or otherwise defined by the investigators) is relatively high and varies in different studies from 63.2% to 100%,[2,5,8-24] which is lower than that of patients with STEMI, but similar to that of cardiogenic shock.[14] Unfortunately, the bleeding complications are not reported uniformly across these studies. Sunde et al have found a non-significant increase in minor bleeding episodes,[25] but Lettieri reports clearly that major bleeding was statistically more frequent among the group of CA patients.[12] Wolfrum et al also observed a tendency for bleeding complications in the subgroup of patients with moderate therapeutic hypothermia ($p<0.08$), with these patients receiving more transfusions than controls ($p<0.04$).[23] Although hypothermia per se has been associated with serious adverse effects such as electrolyte disturbances, arrhythmias and coagulation abnormalities,[26] in a recent study by Batista et al. the combination of PCI and therapeutic hypothermia after CA seems to be safe and effective.[27]

Patient survival in these studies varied between 38% to 81%[2,5,8-24] and it was relatively high in comparison to previous reports,[12] although the endpoints of these studies were different. The major independent predictors of survival were the time interval between the cardiac arrest and the start of cardiopulmonary resuscitation (CPR),[5,12,14,17,20] the existence of a shockable rhythm,[5,12,18,20] early defibrillation,[14] the absence of cardiogenic shock or the need for hemodynamic support with inotropic agents,[12,14,24] the neurological status on admission,[12,18,20,22] and the implementation of PCI.[5,20]

Mager et al compared the mortality of patients with STEMI who survived from CA with the mortality of STEMI patients without CA, after they excluded patients with cardiogenic shock (Table 1).[17] More interestingly, in this study mortality in cardiac arrest patients was exclusively due to non

TABLE 1. Studies in resuscitated patients after cardiac arrest who underwent PCI

Study*	Pts*	Anterior MI*	C/A*	PCI*	TIMI 2-3*	D2B* (min)	IABP*	MTH*	SURVIVAL*	CPC 1-2*
Spaulding et al.[2]	84	N/R	84 (100)	37 (44)	28 (76)	N/R	0	0	32 (38)	N/R
Dumas et al.[5]	435	N/R	435 (100)	202 (46.4)	177 (87.6)	N/R	N/R	370 (85)	171 (39.3)	160 (93.6)
Kahn et al.[8]	11	9 (82)	11 (100)	11 (100)	7 (63.6)	N/R	0	0	6 (54.5)	4 (36.4)
Bendz et al.[9]	40	N/R	40 (100)	40 (100)	38 (95)	52	0	0	29 (72.5)	N/R
Quintero et al.[10]	63	32 (50.8)	63 (100)	63 (100)	56 (88.8)	N/R	0	0	48 (76.2)	N/R
Markusohn et al[11]	25	13 (52)	25 (100)	25 (100)	22 (88)	106	0	2 (8)	19 (76)	17 (68)
Lettieri et al.[12]	99	54 (54.5)	99 (100)	90 (100)	80 (80)	166-172	22 (22)	12 (12)	77 (77.8)	68 (68.7)
Lee et al.[13]	37	23 (62)	37 (100)	36 (97.2)	32 (86.5)	N/R	0	0	30 (81)	25 (67.6)
Garot et al.[14]	186	104 (56)	186 (100)	168 (90.3)	161 (87)	190.7	43	33 (18)	103 (55.4)	99 (53.2)
Peels et al.[15]	44	19 (43.2)	44 (100)	40 (90.9)	38 (86.4)	115	14	0	22 (50)	N/R
Pleskot et al.[16]	26	10 (50)	20 (77)	19 (95)	18 (90)	120	0	0	15 (57.7)	11 (42.3)
Mager et al.[17]	21	14 (67)	21 (100)	20 (95)	20 (95)	96	4 (19)	1 (0.05)	17 (81)	15 (71.4)
Bulut et al.[18]	10	N/R	10 (100)	10 (100)	8 (80)	N/R	0	0	4 (40)	3 (30)
Keelan et al.[19]	15	N/R	15 (100)	14 (87.5)	14 (87.5)	150	6	0	11 (73.3)	9 (60)
Gorjup et al.[20]	117	N/R	117 (100)	109 (93.1)	102 (87.2)	N/R	21 (17.9)	30	93 (79.5)	74 (63.2)
Knafelj et al.[21]	79	N/R	72 (100)	66 (91.6)	64 (96.9)	115-143	15 (19)	40 (50.6)	44 (55.7)	27 (34.2)
Hosmane et al.[22]	98	N/R	78 (79.6)	64 (65.3)	62 (63.2)	104.1	0	3 (3.1)	63 (64)	58 (59.2)
Wolfrum et al.[23]	33	N/R	33 (100)	33 (100)	33 (100)	82-85	12 (36.3)	16 (48.5)	23 (69.7)	19 (57.6)
Anyfantakis et al[24]	72	N/R	72 (100)	25 (34.7)	24 (96)	N/R	16 (22.2)	0	35 (48.6)	33 (45.8)

*Abbreviations: Pts: patients, MI: myocardial Infarction, C/A: Coronary Angiography, PCI: Percutaneous Coronary Intervention, TIMI: Thrombolysis In Myocardial Infarction, D2B: Door to Balloon, IABP: IntraAortic Balloon Pump, MTH: Mild Therapeutic Hypothermia, SURVIVAL: Survival to hospital discharge, CPC: Cerebral Performance Category (normal performance=1, mild disability=2, severe disability=3, vegetative state=4)

cardiac causes (sepsis, $p<0.01$) and this reflects the fact that the survivors from cardiac arrest are those who more often undergo mechanical ventilation, central venous line placement and other interventional procedures that predispose to in-hospital infections. Gorjup et al reported that in survivors of OOHCA who were conscious on admission and subsequently had successful PCI, the long-term prognosis with favorable neurologic outcome was similar to the non-arrest STEMI patients (100% vs. 98%, $p=0.20$).[20]

Of course, these data should be interpreted cautiously. Most studies are retrospective and the number of patients is small and there is a paucity of characteristics that refer to crucial parameters such as time before CPR, time to return of spontaneous circulation (ROSC), etc. Selection bias could also favor PCI, as the patients with worse clinical conditions possibly were not transferred to PCI.

ROUTINE PCI IN SURVIVORS OF CARDIAC ARREST

From the aforementioned studies there is agreement in general that PCI in ROSC patients after STEMI is feasible with high rates of success and with satisfying survival percentage. On the other hand, the usefulness of routine PCI in all survivors of cardiac arrest is under investigation.

After successful return of spontaneous circulation, the resuscitation ECG often demonstrates broad QRS complexes, and is difficult to interpret. Even myocardial enzymes are not reliable, as they could be positive because of the defibrillation attempts. Spaulding et al reports that the prognostic value of the ECG and the history of previous chest pain are not enough to conclude to a definite triage.[2] In particular 9 patients who were transferred to the catheterization laboratory did not have chest pain or ECGs indicative of STEMI and they were finally found to have significant coronary disease. So they conclude that, as the positive and negative predictive value of one of these factors is 0.63 and 0.74 respectively, it should be our intention that all patients with no obvious non cardiac cause of CA should be directed to the catheterization laboratory. However, Voicu et al. assert that the post resuscitation ECG could identify all patients with acute myocardial infarction (AMI) in the setting of CA.[4] They performed routine coronary angiography in 210 patients with OOHCA, regardless of their medical history or ECG abnormalities. The post resuscitation ECG was analyzed retrospectively: ST-elevation only

had moderate sensitivity and specificity, but the combined criterion of ST deviation or broad QRS complexes had a sensitivity of 100%.

A recent study by Anyfantakis et al. argued that PCI could be beneficial only in CA patients with ST elevation.[24] In their study 72 survivors of CA underwent immediate coronary angiography. Although most patients (63.9%) had significant angiographic lesions, only one third (37.5%) had clinical and angiographic evidence of an acute coronary syndrome, such as irregular lesions or acute thrombosis that warranted PCI. However, PCI was not an independent predictor of survival, with younger age, the absence of inotropic support and shorter time to CPR and ROSC, being the strongest correlates.

On the other hand, Werling et al reported that patients who had angiography had statistically higher percentage of survival in 30 days (67% vs. 18%, $p<0.0001$).[28] They concluded further that although a careful evaluation would require randomized control studies, in a population of patients with high incidence of coronary syndromes the need for early coronary angiography cannot be underestimated.

Merchant et al in a retrospective study showed that angiography was not performed in all patients with in-hospital cardiac arrest (IHCA).[29] Many patients with IHCA underwent angiography without ECGs indicative of ST elevation or new LBBB. The incidence of remarkable coronary disease in this subgroup was high and PCI was attempted in 35% (6/17). This study has its own merit, since in-hospital causes of cardiac arrest are different comparing to those of out-of-hospital, as other factors contribute, such as electrolyte disorders, pulmonary embolism or terminal illness. The existence of serious cardiac disease that warrants PCI in this population supports the idea of more aggressive use of angiography among survivors of cardiac arrest with no obvious noncardiac cause.

Finally, Spaulding et al, based on data from the PROCAT registry confirmed his previous findings.[5] Using the largest cohort of OOHCA patients with angiographic records, he assessed whether a strategy of routine PCI improves survival. The number of patients without ST elevation after ROSC, who had significant angiographic lesions, was remarkable (58.5%). Even in the absence of ST elevation, the performance of successful PCI was associated with improved survival (47% vs 31%, $p<0.001$).

The subject of immediate PCI is seriously considered in the recent American Heart Association guidelines for Cardiopulmonary Resuscitation and Emergency Care.[30] Given the high incidence of ischemia in this population and the limitations of the post arrest ECG, medical and interventional treatments are recommended, whenever there is strong suspicion of an acute coronary syndrome (ACS), regardless of the post resuscitation ECG.

NEUROLOGICAL OUTCOME OF CARDIAC ARREST PATIENTS

A large number of patients who survived from cardiac arrest exhibit some form of cerebral dysfunction. In the aforementioned studies the number of patients who had depressed level of consciousness on admission varies from 36%[10] to 88.5%,[16] and there are many issues regarding the stratification of this group. The American Academy of Neurology in a recent article reviewed aspects of the neurological examination, specific biomarkers or electrophysiological studies that could predict the outcome in comatose survivors.[21] The authors express their concern that the neurological examination in such patients is often confounded by factors such as electrolyte disorders, sedation and intubation. They suggest that except for the presence of myoclonus status epilepticus within the first 24 hours, there are no other clinical symptoms or signs that could help clinicians decide which patient will finally awake. They conclude that the most sensitive tool is the continuous clinical evaluation across the first three days after the cardiac arrest episode. On the other hand in acute coronary syndromes, time is myocardium and often there is not much time to wait for the improvement of the neurological status, so the question remains.

Data are still sparse and conflicting due to methodological issues. Some of the previous studies in cardiac arrest STEMI patients reported the neurological outcome of their survivors, mostly with the Glasgow – Pittsburgh Scale (Cerebral Performance Category-CPC). Some authors[18,20,22] reported that the reduced level of consciousness on admission was an independent predictor of poor neurological outcome, as were also the absence of pupil and corneal reflexes,[20] the longer time to ROSC, and older age. On the other hand, Keelan et al have observed in their study, that the majority of patients who were unresponsive on admission have recovered fully at follow up (CPC 1-2).[19] Lettieri et al reported that from the 77 patients who were discharged alive, 67 had recovered fully at follow up.[12] The most interesting point in this study is that from the 20 patients who had Glasgow coma scale-GCS 3 on admission, only 6 exhibited this poor neurologic outcome at follow up. Hosmane et al also report that from the 59 patients who were unresponsive on admission, 44% survived with 88% having full neurological recovery.[22] They stress that serious consideration should be given to primary PCI, regardless of the neurological status.

URGENT PCI: ITS ROLE IN THE CHAIN ON SURVIVAL

Sunde et al observed that despite scientific progress and the continuous education of doctors and paramedical staff, cardiac arrest victims still have unsatisfactory high rates of mortality,[32] that could be attributed at least in part to the poor post resuscitation care. For that reason, they designed a standardized post resuscitation treatment protocol for

OOHCA that included intensive hemodynamic, blood glucose, electrolyte and seizure control, hypothermia and early PCI when indicated.[25] They compared the outcome of CA patients in that "intervention" period with CA populations in the preceding years. They found that patients in the former group had improved survival (56% vs. 31%, p=0.007) with similarly improved neurological outcome (56% vs. 26%, p=0.001) at hospital discharge, that was also sustained over one year of follow up (56% vs. 26%, p=0.001). Among factors that contributed to the improved outcomes was of course the implementation of early PCI.

Lund-Kordahl et al studied the temporal changes and trends in the management of OOHCA survivors across three distinct time periods in the city of Oslo.[33] They observed that across these three successive time periods, 1996-1998, 2001-2003, 2003-2005, there was a statistically significant increase in survival (7%vs. 10% vs. 13%, p=0.001) with a similar favorable neurological outcome (6% vs. 9% vs. 12%, p=0.001). The authors assumed that the improvement, especially in the third period, was due to the intensive post resuscitation methods, with the utilization of PCI included. The purpose of the aforementioned two studies was not to evaluate the role of PCI, rather to stress that the after-arrest care is the weak link in the chain of survival.

CONCLUSIONS

Patients with cardiac arrest comprise a group of patients with increased mortality and special characteristics that require urgent management. Review of the literature demonstrates that performance of urgent angiography and PCI in patients who recovered from CA is possible, has increased rate of success and is compatible with increased survival.

In the group of CA patients with STEMI, new LBBB or history of chest pain, urgent PCI aiming to open the infarcted artery is the indicated therapeutic strategy. As the incidence of coronary heart disease among the cardiac arrest population is high, recent guidelines support that urgent PCI could also be beneficial in patients with cardiac arrest of no obvious noncardiac cause, even if they do not demonstrate clinical or ECG criteria of ischemia. On the other hand there is a large number of resuscitated patients with varying degrees of neurological disability. As there is no reliable prognostic tool, at least in the limited time period in which PCI is applicable, the decision to perform PCI in a comatose patient can only be made on an individual basis. Finally, the role of PCI in the post resuscitation period cannot be viewed in isolation, but only through an organized treatment strategy that includes early recognition of CA victims, early initiation of CPR, early defibrillation and intensive post resuscitation care.

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