REVIEW

Post resuscitation care
What are the therapeutic alternatives and what do we know?

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A large proportion of deaths in the Western World are caused by ischaemic heart disease. Among these patients a majority die outside hospital due to sudden cardiac death. The prognosis among these patients is in general, poor. However, a significant proportion are admitted to a hospital ward alive. The proportion of patients who survive the hospital phase of an out of hospital cardiac arrest varies considerably. Several treatment strategies are applicable during the post resuscitation care phase, but the level of evidence is weak for most of them. Four treatments are recommended for selected patients based on relatively good clinical evidence: therapeutic hypothermia, beta-blockers, coronary artery bypass grafting, and an implantable cardioverter defibrillator. The patient’s cerebral function might influence implementation of the latter two alternatives. There is some evidence for revascularisation treatment in patients with suspected myocardial infarction. On pathophysiological grounds, an early coronary angiogram is a reasonable alternative. Further randomised clinical trials of other post resuscitation therapies are essential.

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Background
A large proportion of deaths in the Western World are caused by ischemic heart disease. Among these patients a majority die outside hospital due to sudden cardiac death.1

The prognosis among these patients is, in general, poor.1 However, a significant proportion are admitted to a hospital ward alive: 20–35% in Scandinavian studies.2–4 This means that about 125 patients per million inhabitants require post resuscitation care each year. If survivors from in hospital cardiac arrest are included, the number of patients requiring post resuscitation care is double this figure.4

The proportion of patients who survive the hospital phase of an out-of-hospital cardiac arrest varies considerably.3–5 From large patients series it has been shown that between 30 and 60% can be discharged from hospital alive.3–5 The cerebral function of these patients is also highly variable.4

Predictors for outcome
Survival with complete neurological recovery depends on several interventions during the chain of survival and includes both pre- and post admission factors. Preadmission factors cannot be influenced by the post resuscitation care. They include increasing age, a previous history of diabetes or heart failure and various factors related to the resuscitation event: Initial rhythm, whether the arrest was witnessed or not, bystander CPR, time of first defibrillation attempt for patients in ventricular fibrillation,2 and the duration of arrest, i.e. the severity of the ischaemic insult to the brain.6
The patient’s status on admission to hospital is a very important determinant of outcome; factors to consider include: level of consciousness, presence of cardiogenic shock and presence of sinus rhythm. Prehospital post resuscitation care therefore is important and may influence outcome significantly, but only a few studies exist.

Post admission factors and the final outcome are influenced significantly by the quality of post resuscitation care, which differs among hospitals. Treatment of both the global ischaemic brain damage and the dysfunctional heart during the reperfusion phase is the main challenge. The post-resuscitation phase is associated with a sepsis-like syndrome, with high levels of circulating cytokines, adhesion molecules, plasma endotoxin and unregulated leukocyte production of cytokines.

Several post admission factors have been highlighted recently. Langhelle et al. reported four factors that were associated with an adverse outcome: elevation of serum glucose (>10.7 mmol/l), pyrexia (>37.8°C), acidosis (base access ≤−3.5 mmol/l), and seizures. Skrifvars et al. identified the following to be associated with an adverse outcome: elevation of serum glucose >6.8 mmol/l, absence of treatment with beta-blockers, and serum potassium >4.2 mmol/l.

With the exception of temperature control, which is an established post-resuscitation therapy, a cause and effect relationship was not investigated and should be the focus of further interventional studies.

Therapeutic possibilities (Table 1)

The therapeutic strategies that can be adopted in the post-resuscitation period can be divided into four main categories:

1. Optimising physiology/general intensive care treatment;
2. Revascularisation;
3. Anti-arrhythmic therapy;
4. Anticonvulsant therapy.

The four categories include 13 topics. The levels of evidence are defined as: (A) data derived from multiple randomized clinical trials; (B) data derived from a single randomized clinical trial or non-randomized studies; and (C) expert consensus or data derived from small studies.

Optimizing physiology/general intensive care treatment

Body temperature

The role of therapeutic hypothermia in post resuscitation care has been investigated extensively during the last decade. Two randomized trials of moderate size published in 2002 strongly support the use of therapeutic hypothermia in comatose patients admitted to hospital after witnessed out of hospital ventricular fibrillation cardiac arrest. A recent published meta-analysis and systematic review gives further evaluation evidence. In the larger of these two trials from 2002, 273 patients were randomized to be treated with either therapeutic hypothermia (32–34°C for 24h) or normothermia. Fifty-five percent of the patients in the hypothermia group were discharged alive with a good neurological outcome versus 39% in the group who were treated conventionally (p = 0.009). Therapeutic hypothermia may also be beneficial for other primary rhythms. If therapeutic hypothermia is contraindicated, hyperthermia, which is common during the first 24 hours after cardiac arrest, must be avoided.

Indication for hypothermia

Patients remaining comatose after return of spontaneous circulation following a witnessed ventricular fibrillation cardiac arrest should receive therapeutic hypothermia management (level of evidence A).

Blood pressure

There are few randomized trials evaluating the role of blood pressure on the outcome after out
of hospital cardiac arrest. One randomized study demonstrated no difference in the neurological recovery of patients randomized to a mean arterial blood pressure of >100 mmHg versus ≤ 100 mmHg 5 min after return of spontaneous circulation. However, good functional recovery was associated with a higher blood pressure during the first 2 h after return of spontaneous circulation. In a similar study of patients with out-of-hospital ventricular fibrillation, Herlitz et al. reported higher mortality if the systolic blood pressure was below 120 mmHg on hospital admission. On the other hand, a recent study of survivors of out-of-hospital cardiac arrest monitored using pulmonary artery catheters showed that hypotension and myocardial dysfunction is common during the first 24 h but not predictive of survival or neurological recovery. Despite a significant improvement in cardiac index at 24 h, continued vasodilatation delayed the discontinuation of vasoactive drugs, and the myocardial dysfunction was reversible only in the survivors. Myocardial dysfunction, a result of global myocardial stunning, is well described in several studies and may be improved by dobutamine at 5 μg/kg/min.

**Indication for optimizing blood pressure**
Based on the available data, severe hypotension and hypertension should be avoided (level of evidence C).

**Blood glucose**
An infusion of glucose and insulin improves cerebral outcome after asphyxial cardiac arrest in rats and in an intervention study with glucose infusion before complete cerebral ischaemia in monkeys, lower blood glucose levels were associated with better outcome. Intensive insulin therapy improves outcome among surgical patients in the intensive care unit. A recent trial of insulin therapy in critically ill patients indicated that control of glucose levels, with a target level of less than 8.0 mmol/l, rather than the dose of exogenous insulin therapy accounts for the improved survival.

In the DIGAMI study, the infusion of glucose and insulin followed by long-term insulin improved long-term outcome among diabetic patients with acute myocardial infarction; however, this has not been confirmed in the more recent DIGAMI Z study. The latter study did, however, demonstrate that elevation of blood glucose is an independent predictor for an adverse outcome among diabetic patients with a threatened myocardial infarction.

**Indication for optimizing blood glucose**
Hypo- and hyperglycaemia should be avoided. The threshold blood glucose value that should trigger insulin therapy is unknown but is likely to be in the range 6.1–8.0 mmol/l (level of evidence C).

**Acid–base status**
There is no randomized trial evaluating the possible benefit of treating acid–base disturbances; however, acidosis per se is an adverse prognostic factor in the post resuscitation phase.

**Indication for optimizing acid–base status**
Undetermined; although avoidance of severe acidosis is reasonable (level of evidence C).

**Serum potassium**
There is no randomized trial evaluating the value of changing serum potassium in post resuscitation care; however, hyperkalaemia is an adverse prognostic factor among these patients. Whether or not this is an epiphenomenon of acidosis or renal insufficiency is uncertain.

**Indication for optimizing serum potassium**
Based on previous experiences it is reasonable to recommend avoidance of hyperkalaemia and avoidance of hypokalaemia (level of evidence C).

**Serum magnesium**
Hypomagnesaemia is associated with adverse outcome in critically ill patients and may have a role in mitigating neurological injury; however, there is no randomization trial evaluating magnesium in post-resuscitation care.

**Indication for optimizing serum magnesium**
Avoid hypomagnesaemia (level of evidence C).

**Revascularization**
A post mortem study of 82 cardiac arrest victims in Finland, indicated that coronary artery disease was the cause of the arrest in 78% and furthermore, coronary thrombi are found frequently in patients after sudden cardiac death. Acute changes in coronary plaque morphology are found in 40–86% cardiac arrest survivors, and in 15–64% in autopsy studies.

Immediate coronary angiography among survivors of out of hospital cardiac arrest showed a
coronary occlusion in 48% of cases; not all patients had an ECG-pattern indicating such a finding.35

**Thrombolysis**

There are limited data on the impact of thrombolysis on survival during the post resuscitation period. An observational study of relatively few patients (n = 69) showed a survival benefit for thrombolysis36: the mortality was 13 of 33 (39%) among those receiving thrombolysis versus 24 of 36 (67%) in those who did not. The difference was in deaths attributed to cardiac, rather than neurological causes.36 Similar findings are reported from Finland,10 Sweden,19 Great Britain37 and Germany.38 Although bleeding has been reported in a few cases,37,38 thrombolysis seems to cause few side-effects, even when given in the prehospital setting.19

**Indication for thrombolysis**

In-hospital thrombolysis is recommended for patients with ST-elevation who have not received pre-hospital thrombolysis if there are no facilities for immediate percutaneous transluminal coronary intervention (PCI) (level of evidence C).

**Percutaneous transluminal coronary intervention**

Sixty of 84 (71%) out of hospital cardiac arrest survivors undergoing immediate coronary angiography had significant coronary artery disease.35 PCI was attempted in 37 patients and successful in 28 patients; the overall survival rate was 38%. Successful PCI was an independent predictor for an increased survival.35 Similarly, Bendz et al. reported almost 70% survival in 40 cardiac arrest patients arriving at the hospital after primary successful cardiopulmonary resuscitation,39 showing the practical approach and perhaps benefit for this intervention on these patients.

**Indication for PCI**

PCI is indicated when cardiac arrest is thought to be caused by myocardial ischaemia/infarction and a culprit lesion is found at coronary angiography (level of evidence C).

**Coronary artery bypass grafting (CABG)**

There is no randomized trial evaluating the impact of CABG on survival in the post resuscitation phase. In an observational study with 5 year follow up of immediate survivors of out of hospital cardiac arrest, 26% of 85 patients undergoing CABG had cardiac arrest or died versus 62% among 180 who were on medication without surgery. When adjusting for differences at baseline, CABG was associated with a significant reduction in the risk of a new cardiac arrest, but not death.40

Randomized clinical trials41—43 and meta-analysis44 have shown that among patients with angina pectoris and a left main stenosis or three vessel coronary artery disease, CABG will improve survival.

**Indication for CABG**

Coronary artery bypass grafting is indicated in the post resuscitation phase for patients with left main stenosis or triple vessel coronary artery disease if the cardiac arrest was thought to be caused by ischaemic heart disease (level of evidence A or C depending on interpretation).

**Anti-arrhythmic therapy**

**Implantable cardioverter defibrillator (ICD)**

Previous experiences indicate that among patients with acute myocardial infarction and depressed systolic myocardial function (ejection fraction less than 35%) treatment with an ICD, compared with antiarrhythmic therapy, will improve prognosis during long term follow up.45 Some of these patients had sustained a cardiac arrest before randomisation; however, three secondary prevention ICD trials have evaluated the impact of this device on survival among patients having suffered from a previous cardiac arrest. The first of these, the antiarrhythmic versus implantable defibrillator (AVID) study included patients with prior ventricular fibrillation as well as patients with haemodynamically unstable ventricular tachycardia.46 One thousand and sixteen patients were randomised to receive either an ICD or drug therapy: either amiodarone or sotalol. Over a mean follow up of 18 months, death rates were 15.8 ± 3.2% for the ICD versus 24.0 ± 3.7% for drug therapy (p < 0.02). The prolongation of life was modest — just over 3 months.

The Cardiac Arrest Study Hamburg (CASH) trial enrolled patients with prior ventricular fibrillation and recruited patients into three arms: ICD (n = 99); amiodarone (n = 92); and metoprolol (n = 97).47 Over a mean follow up period of 57 months therapy, an ICD was associated with a 23% (non-significant) reduction in all cause mortality rates compared to treatment with amiodarone/metoprolol.

The Canadian Implantable Defibrillator Study (CIDS) enrolled patients with prior ventricular
fibrillation as well as patients with haemodynamically unstable ventricular tachycardia and patients with reduced left ventricular function, syncope and inducible ventricular tachycardia. Six hundred and fifty-nine patients were assigned randomly to treatment with an ICD or with amiodarone. At 5 years a non-significant reduction in the risk of death was observed with the ICD (8.3% per year) compared with 10.2% per year in the amiodarone group (a relative risk reduction of 20%).

A meta-analysis of the three trials showed a significant reduction in death from any cause with an ICD with a summary hazard ratio of 0.72 (95% confidence interval 0.60—0.87; p=0.0006). The ICD extended survival by a mean of 4.4 months during a follow up period of 6 years. Patients with a left ventricular ejection fraction \( \leq 35\% \) derived significantly more benefit from ICD therapy than those with better left ventricular function.

**Indication for ICD**
The balance of evidence favours ICD-therapy over anti-arrhythmic medical therapy (level of evidence A or B).

**Beta-blockers**
Beta-blockers reduced total mortality (particularly sudden death) among patients with myocardial infarction and/or heart failure and are associated with improved survival in cardiac arrest registries. The indications for beta-blockers are (1) Known or recent myocardial infarction and/or heart failure (level of evidence A or C); (2) cardiac arrest of presumed cardiac aetiology (level of evidence B).

**Amiodarone**
The two largest trials evaluating patients at risk of sudden death showed that amiodarone reduced arrhythmic deaths but not the total deaths. Meta-analysis from all 13 randomised controlled trials of amiodarone (89% after myocardial infarction) showed a significant reduction in total mortality and a significant reduction in arrhythmic death.

**Indication for amiodarone**
Recurring ventricular arrhythmias despite beta-blockade or if beta-blockade is not tolerated (level of evidence C).

**Anticonvulsant therapy**
Seizures occur after cardiac arrest in up to 30—40% of cases and are associated with a worse outcome. Early prevention and treatment of seizures is advocated although the scientific evidence for this strategy is weak; the link between seizures and outcome may be causative or simply an epiphenomenon. Anticonvulsants such as thiopental and especially phenytoin are neuroprotective, but a clinical trial of thiopental after cardiac arrest showed no benefit. Further clinical studies are required.

**Indication for anticonvulsants**
The indication for anticonvulsants is undetermined, although treatment of seizures is reasonable (level of evidence C).

**Conclusion**
Several treatment strategies are applicable during the post resuscitation care phase, but the level of evidence is weak for most of them. Four treatments are recommended for selected patients based on relatively good clinical evidence: therapeutic hypothermia, beta-blockers, coronary artery bypass grafting, and an implantable cardioverter defibrillator. The patient’s cerebral function might influence implementation of the latter two alternatives. There is some weak evidence for revascularisation treatment in patients with suspected myocardial infarction. On pathophysiological grounds, an early coronary angiogram is a reasonable alternative. Further randomised clinical trials of other post resuscitation therapies are essential.

**References**
resuscitated by the same Emergency Medical Service and admitted to one intensive care unit over a 16-year period in the municipality of Göteborg. Resuscitation 2000;43:201–21.


