Reperfusion therapy in out-of-hospital cardiac arrest: Current insights

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Summary Although early care in out-of-hospital cardiac arrest has been improved over the past decades, survival remains poor and neurological performance after survival is often impaired. Consequently, new therapies are needed to improve outcome. As thrombotic processes such as acute myocardial infarction or pulmonary embolism are frequent causes of cardiac arrest, therapies like fibrinolysis or percutaneous coronary intervention are of interest. Both therapies can restore coronary and pulmonary perfusion in cardiac arrest patients and, additionally, fibrinolysis might prevent microthrombi to the brain. In this review, the rationale, safety and efficacy of reperfusion therapy in patients with out-of-hospital cardiac arrest will be discussed.

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Introduction

Cardiovascular disease is a major health problem in Western countries. Cardiac arrest is the first presentation in about 25%. In Europe, approximately 275,000 patients per year experience a cardiac arrest outside the hospital as a result of coronary artery disease, and undergo an attempt at cardiopulmonary resuscitation (CPR). The survival rate to hospital discharge is extremely low for out-of-hospital cardiac arrest and averages around 7%. Time is an important determinant of survival. For example, in patients suffering from ventricular fibrillation the chance of survival is reduced by a relative 7—10% with every minute delay to therapy. Care for cardiac arrest patients has been improved, mainly resulting in earlier initiation of therapy, the so-called optimised chain of survival: early access, early basic life support by a bystander, early defibrillation and early advanced cardiac life support. Despite these improvements, survival rates after cardiac arrest did not really increase as has been shown by several large registries. In the case of survival neurological status is often impaired. Therefore, new therapies and strategies are being explored to improve outcome after cardiac arrest. As most cardiac arrests are the result of thrombotic processes, such as acute myocardial infarction or pulmonary embolism, reperfusion with fibrinolysis or percutaneous intervention is one of the therapies of interest. Although fibrinolysis has always been considered relatively contraindicated, there is increasing clinical evidence that this strategy might be relatively safe and beneficial. Also, there is evidence that percutaneous intervention might be beneficial in selected cardiac arrest patients. Both reperfusion strategies will be discussed in this article.

The role of fibrinolysis in cardiac arrest

Out-of-hospital cardiac arrests have both cardiac and non-cardiac causes (Figure 1). It is estimated that coronary artery disease is the leading cause of cardiac arrest: 50—70% of cases are due to acute myocardial infarction (or ischaemia) triggering a life-threatening ventricular arrhythmia. Massive pulmonary embolism is a second thrombotic cause, responsible for approximately 5% of cardiac arrests, which should especially be suspected when pulseless electrical activity or asystole is the presenting rhythm. These estimates are based on retrospective studies using autopsy or coronary angiography to verify the cause of the arrest. Since thrombotic processes are the most frequent cause of cardiac arrests, fibrinolysis could be beneficial. In patients with acute myocardial infarction and selected patients with pulmonary embolism, fibrinolysis has been shown efficacious in a setting without CPR. Moreover, a potential additional effect of fibrinolysis lies in the prevention of microthrombi in the brain in cardiac arrest patients. However, there has always been fear of an increased risk of clinically important bleeding complications.

Safety of fibrinolytic therapy in cardiopulmonary resuscitation

To date, both European and American guidelines describe traumatic CPR as a relative contraindication for the use of fibrinolysis. The American guidelines additionally describe prolonged CPR (10 min) as contraindication because of fear of severe bleeding complications. This seems plausible because fibrinolytic treatment for myocardial infarction or pulmonary embolism without the need for CPR is associated with an increased bleeding risk in comparison with controls. For example, in a large meta-analysis of patients with myocardial infarction not complicated by cardiac arrest, a three-fold increase in life-threatening bleeding or bleeding requiring transfusion was found in fibrinolytic treated patients compared with control patients during the first 35 days (OR 2.9, 95% CI 2.4—3.7). Intracranial haemorrhage was found in 0.8% of fibrinolytic treated patients and in 0.1% of controls. Based on the analysis, the American guidelines advice against fibrinolysis in patients undergoing CPR, although
no subgroups of patients undergoing CPR were analysed.\textsuperscript{16}

In cardiac arrest patients, without treatment with fibrinolysis bleeding is expected to occur in approximately 10—15\% of cases.\textsuperscript{19} It is estimated that in approximately one third of these cases of bleeding is the cause of the arrest. The question is whether or not additional treatment with fibrinolysis leads to an increased bleeding risk in cardiac arrest patients undergoing CPR.

**Safety in cardiac arrest with confirmed acute myocardial infarction**

Tables 1a and 1b shows bleeding and survival rates for two observational studies published in the early 90s.

All patients were diagnosed with acute myocardial infarction and treated with fibrinolysis. Bleeding rates were compared between patients with or without cardiac arrest and were found to be similar. No intracranial haemorrhages occurred.\textsuperscript{20,21} Another study addressed bleeding complications in a retrospective cohort of 265 patients with out-of-hospital cardiac arrest caused by myocardial infarction who were admitted after successful resuscitation. Of the 132 patients receiving rt-PA after myocardial infarction was diagnosed, 10\% suffered from major bleeding. Intracranial haemorrhage was found in two of these patients. In the 133 control patients major bleeding occurred in 5\% and intracranial haemorrhage was found in one of these patients. None of the bleeding episodes caused death. Multivariate analysis showed that fibrinolysis seemed associated with a more than twofold increased bleeding risk (OR 2.5, CI 0.9—7.4). For conclusions with respect to an impact on survival, numbers were too small (OR 1.6, CI 0.0—3.0). A longer duration of CPR was not associated with an increased risk of bleeding.\textsuperscript{22}

**Safety in cardiac arrest with confirmed pulmonary embolism**

In a retrospective study major bleeding complications in pulmonary embolism requiring CPR were
analysed (Tables 1a and 1b). Thirty-six pulmonary embolism patients who received fibrinolysis in the setting of a cardiac arrest were compared with 30 patients who did not. Again, a two-fold increased risk of major bleeding in fibrinolytic treated patients was observed (OR 2.5, CI 0.8—8.6), and the point estimate of fibrinolysis for survival seemed to indicate a potential benefit (OR 2.9, CI 0.8—13.8). Again, in contrast to the statements in the guidelines, no association between the duration of CPR and occurrence of bleeding was found.23

Safety in cardiac arrest with a presumed cause

One retrospective study provided data on bleeding complications in 91 patients with detailed autopsy. Forty-five patients received rt-PA and 46 did not. In the first group, six patients had severe bleeding complications, compared to seven in the second group. In both groups, one intra-cerebral haemorrhage and two ruptured aortic aneurysms were found. In the rt-PA group, two patients had a pericardiac tamponade and one had a haemothorax. In the control group, pericardiac tamponade was found in three patients and a subarachnoidal haemorrhage in one patient.24 From a recent safety review of 50 case reports or series and 17 retrospective or prospective studies it can be concluded that fibrinolysis tended to increase the bleeding complications, but that the majority could be treated effectively.19 A meta-analysis of studies comparing CPR with and without fibrinolysis strongly supports the increased risk. A more than twofold increase in major bleeding was found if patients were treated additionally with fibrinolysis: 9.9% versus 3.4%.25 In conclusion, bleeding complications in cardiac arrest patients occur frequently and fibrinolytic treatment increases the risk of bleeding. This risk does not seem to be related to the duration of CPR. The question is whether the benefit of fibrinolysis outweighs the risk.

Rationale of fibrinolysis in cardiac arrest

Myocardial infarction and cardiac arrest

The incidence of acute myocardial infarction is approximately 2–3 per 1000 in Western countries and the in-hospital mortality is about 10%.26 Importantly, the true mortality rate is substantially higher, since many patients do not survive to hospital admission. One of the categories among these patients is those presenting with a cardiac arrest.

The majority of these patients will present with ventricular arrhythmias. Typically, impending ST-elevation myocardial infarction is characterised by an acute thrombotic occlusion of a coronary artery resulting in an area of transmural ischaemia. This can lead to electrical inhomogeneity, providing the substrate for micro re-entry pathways triggering ventricular fibrillation.27 In a setting without CPR, reperfusion therapy has been proven of paramount importance to minimise myocardial damage and preserve left ventricular function, with the largest benefits when administered early after symptoms.28 In that respect, patients with a cardiac arrest might benefit in particular since they often present within the first hour after myocardial infarction.27,29 However, in many cases infarctions are caused by subtotal thrombotic occlusion of a coronary artery, i.e. non-ST-elevation myocardial infarction, which can also present as a cardiac arrest. In a setting without the need for CPR, fibrinolytic therapy has not been proven efficacious and could even be harmful in non-ST-elevation myocardial infarction.30

Based on these findings, one would, preferably, only administer fibrinolysis in case of ST-elevation myocardial infarction during a cardiac arrest. However, in the acute phase, the diagnosis of myocardial infarction is not easily established, and differentiation between ST-elevation and non-ST-elevation myocardial infarction is even more
difficult. With every passing minute, the prognosis decreases, and the classic diagnostic criteria, such as medical history, findings on the electrocardiogram (ECG) and cardiac enzymes or biomarkers are of limited use in the acute phase of a resuscitation. First, in the setting of an arrest, chest pain and the presence of ST-elevation have been shown to be poor predictors of acute coronary occlusion. Conversely, the absence of these findings does not rule out an acute occlusion. Second, although Q-waves are often indicative of transmural ischaemia, they can represent acute as well as old myocardial infarction. Third, myocardial damage in ST-elevation and non-ST-elevation myocardial infarction is normally reflected by elevated creatine kinase MB and troponin levels, which can only be measured after approximately 6 h. A major limitation is that ventricular arrhythmias develop mostly within the first hour after an acute occlusion and cardiac enzymes or biomarkers are therefore typically negative. Another problem could be that cardiac enzymes and markers may turn out to be positive due to chest compressions and defibrillation, although several studies state that this is not the case for troponin. Some observational studies with selected patients report that in case of elevated troponin, myocardial infarction is highly likely.

In view of the need for very early initiation of treatment, and the inherently limited time for the diagnostic process, a distinction between the two entities of myocardial infarction is too cumbersome. Moreover, the lack of benefit of fibrinolytic therapy in non-ST-elevation myocardial infarction is derived from patients who were haemodynamically stable, thus without need for CPR, with a rather good a priori prognosis. Patients undergoing CPR have a very poor prognosis, and based on their haemodynamic status one could assume that the combination of an anatomically subtotal thrombotic coronary occlusion and low flow could result in a functionally total occlusion, and so fibrinolysis might have a positive impact. On the other hand, in some patients with non-ST-elevation myocardial infarction, myocardial damage is thought to be related to thrombotic dispersion, which could provide the substrate for ventricular fibrillation given the possibility of different small electrical islets throughout the myocardium. Whether fibrinolysis may be of benefit is uncertain, and remains to be determined.

Besides thrombotic causes, also non-thrombotic causes should be suspected in a cardiac arrest patient. In analogy to the difficulty in differentiation between the type of infarction, the distinction between thrombotic and non-thrombotic causes is also rather difficult in the acute situation. An important non-thrombotic cause of ventricular tachycardia or ventricular fibrillation is the presence of a myocardial scar from a previous myocardial infarction in patients with impaired left ventricular function. In these patients with previous myocardial infarction and the absence of an acute subtotal thrombotic occlusion, the presence of surviving myocytes in scarred tissue forms the substrate for macro re-entry pathways. These can cause ventricular tachycardia, which could potentially degenerate into ventricular fibrillation. In these patients, it is questionable whether fibrinolysis may do more good than harm.

Given the paramount importance of every passing minute, the diagnostic process should not be delayed and since at least 50% of cardiac arrests are the result of a total coronary occlusion, the generalised application of fibrinolysis seems to be the preferred strategy and can be of value for many patients. This generalised application implies that patients with other than thrombotic aetiologies underlying the arrest will receive fibrinolysis, which may result in a different efficacy of reperfusion therapy compared to the impact observed for those with a thrombotic origin of the arrest.

**Pulmonary embolism and cardiac arrest**

The incidence of pulmonary embolism not complicated by cardiac arrest is 1 per 1000 per year and the mortality rate is high, up to 17.5% in 3 months. Fibrinolysis is recommended in confirmed pulmonary embolism, complicated by haemodynamic instability (tachycardia, shock, hypotension or syncope) and/or severe right ventricular dysfunction. This recommendation is based on subgroup analyses of small and unblinded randomised trials in which the majority of patients studied suffered from pulmonary embolism without haemodynamic consequences. In pulmonary embolism without these complications and with normal right ventricular function the clinical need to administer fibrinolysis is uncertain, and its benefit is difficult to demonstrate as the prognosis is fairly good (5% 3-month mortality). Pulmonary embolism is the cause of cardiac arrest in approximately 2–7% of all cases and is encountered more often in patients presenting with pulseless electrical activity compared to patients presenting with asystole or ventricular fibrillation. Whenever cardiac arrest occurs after confirmed pulmonary embolism, the mortality ranges from 65 to 95%. The mechanisms causing cardiac arrest are based on obstruction of the right ventricle by the embolism. This increases the workload and oxy-
Fibrinolytic therapy, cerebral reperfusion and neurological outcome

Whereas in the acute phase the presenting rhythm and underlying condition are predictive for initial survival, prolonged survival is more dependent on the neurological status of the patient. The brain is intolerant of prolonged periods of low or absent blood flow. Inadequate blood flow results in hypoxia and ischaemia of the brain. The neurological status of the patient. The brain is intolerant of prolonged periods of low or absent blood flow. Inadequate blood flow results in hypoxia and ischaemia of the brain.

Brain damage causes poor neurological outcome and is associated with increased mortality. In case of survival, at best 80% of patients will have an acceptable neurological outcome.41

The concept of neuronal cell death is not exactly known, but several mechanisms are involved. Impaired blood flow leads to increased blood viscosity, activation of coagulation and platelet aggregation, which can contribute to the formation of microthrombi. These thrombi can obstruct the cerebral microcirculation, contributing to neuronal cell death. Moreover, the arrest triggers an inflammatory response with leukocyte recruitment and oedema of brain cells. Experimental data suggest that free oxygen radicals can develop in this prothrombotic and inflammatory environment which can induce cell injury and apoptosis. These processes occur not only due to impaired or absent blood flow during the CPR, but also after restoration of perfusion as an ischaemic reperfusion injury.

Several studies have been performed addressing these processes in more detail. To start with the activation of blood coagulation, a human study in which blood samples during CPR and up to 72 h after restoration of circulation were taken, showed that the activity of the coagulation system was markedly increased during and after prolonged CPR (median of 30 min) and was not adequately counteracted by endogenous fibrinolysis. This may lead to the formation of microthrombi and contribute to perfusion disorders, the cerebral microcirculation included.

Data suggesting impaired microcirculation were derived from a study in which the cerebral microcirculation was compared between two groups of rats after induced ventricular fibrillation by electrical stimulation. The rats were subjected to 12 min of cardiac arrest, followed by 5 min of chest compressions and ventilation, or to 17 min of cardiac arrest only. After defibrillation and adrenaline (epinephrine), the circulation was restored in 50% of both groups. In both groups, the cerebral microcirculation was impaired, but interestingly cerebral microcirculation was more often impaired in the group of rats receiving chest compressions as was shown by more and larger areas of absent capillary filling.39

Why chest compressions, representing a low-flow state, result in larger areas of absent capillary filling remains unexplained.

Notably, human studies show that the performance of chest compressions is essential to provide some perfusion of vital organs and that bystander CPR is associated with increased survival. Based on the experimental data, it can only be inferred that during and after cardiac arrest a prothrombotic milieu exists in which microthrombi can develop, indicating a role in the aetiology of microvascular (re)perfusion disorders and neurological outcome. Therefore, preventing or dissolving microthrombi might improve neurological outcome. This could be a second mechanism targeted by fibrinolysis that might result in improved prognosis in cardiac arrest patients.

Confirmation was found in a study conducted in cats submitted to 15 min of cardiac arrest followed by CPR (chest compressions, adrenaline and defibrillatory shocks). Half of them received heparin combined with an rt-PA bolus followed by infusion whereas the other half did not. All cats were successfully resuscitated after 6 min of CPR, followed by 30 min of spontaneous circulation. Thereafter, absence of microvascular filling was studied in the forebrain. Interestingly, in rt-PA treated cats absence of microvascular filling was found in 7%, whereas in untreated cats it was 28%. Possibly, the reduced cerebral damage is related to improved cerebral blood flow by preventing or dissolving microthrombi.15 Although promising, these data are experimental and there is no evidence in humans that these processes occur during cardiac arrest, but it seems logical.

In animals, microcirculatory cerebral blood flow is used as a surrogate marker for neurological function. In humans, the cerebral performance category (CPC) is applied to score resuscitated patients neurolologically. This score is often used as an indicator of neurological damage, which could be related to cerebral perfusion disorders (Table 2). The CPC was used in a retrospective analysis of 157 patients suffering from cardiac arrest presenting with ventricular fibrillation caused by myocardial infarction. Forty-two patients received fibrinolysis and in com-
Table 2  Cerebral performance categories (CPC)

<table>
<thead>
<tr>
<th>CPC</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPC 1</td>
<td>Good cerebral performance. Conscious. Alert, able to work and lead a normal life. May have minor psychological or neurological deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities)</td>
</tr>
<tr>
<td>CPC 2</td>
<td>Moderate cerebral disability. Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dressing, travelling by public transportation, and preparing food). May have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes</td>
</tr>
<tr>
<td>CPC 3</td>
<td>Severe cerebral disability. Conscious. Dependent on others for daily support because of impaired brain function (in an institution or at home with exceptional family effort). At least limited cognition. Includes a wide range of cerebral abnormalities from ambulatory with severe memory disturbance or dementia precluding independent existence to paralytic and able to communicate only with eyes, as in the locked-in syndrome</td>
</tr>
<tr>
<td>CPC 4</td>
<td>Coma, vegetative state. Not conscious. Unaware of surroundings, no cognition. No verbal or psychological interactions with environment</td>
</tr>
<tr>
<td>CPC 5</td>
<td>Certifiably brain dead or dead by traditional criteria</td>
</tr>
</tbody>
</table>

Comparison with patients receiving standard care a good neurological recovery (CPC 1 and 2) was found more often: 69% versus 50%, respectively. When adjusting for age, adrenaline dosage and CPR-duration a trend towards good neurological outcome was found in favour of fibrinolysis. Similar results were found in a long-term follow-up study showing promising neurological outcome, level of performance and subjective well-being in 27 survivors of 108 rt-PA treated patients. Eighty-one percent of patients discharged alive had no neurological deficit (CPC 1). Fifty-six percent of patients were able to manage their pre-arrest level of activity. Additionally, in several case series 80–95% of patients surviving after cardiac arrest had a good neurological outcome after thrombolytic therapy. Because the evidence is based on experimental, retrospective and uncontrolled data, future trials especially designed to study neurological outcome are needed.

Efficacy of fibrinolysis in cardiac arrest

Cardiac arrest and confirmed acute myocardial infarction

More than a decade ago fibrinolysis was already considered an acceptable therapy in patients who presented with myocardial infarction and in whom subsequently CPR was required. Nonetheless, in these patients fibrinolysis was also considered potentially harmful: the risk of fatal haemorrhage was thought to be increased considerably. In most of the individual trials, fibrinolysis showed a non-significant increase in the risk of bleeding (Table 1). A recent meta-analysis of these kind of studies showed a significant two-fold increase of bleeding (OR 2.2, 95% CI 1.3–3.9). Despite this increased risk of bleeding, fibrinolysis was associated with a doubled rate of survival to discharge (OR 2.0, 95% CI 1.2–3.3). Nonetheless, because publication bias could have influenced the results, these should be interpreted cautiously.

With respect to efficacy, potential benefit of fibrinolysis in patients with confirmed myocardial infarction is shown in Table 3. Although these data are derived from observational studies and do not indicate significant differences in all individual trials, all-point estimates are in the same direction and meta-analysis seems to indicate that fibrinolysis is efficacious.

In the Myocardial Infarction Triage and Intervention Registry, 599 of the 12,984 patients suffering from myocardial infarction were resuscitated prior to hospital admission. In total, 53 of the 599 patients received fibrinolysis, 59 percutaneous coronary intervention and 487 did not receive reperfusion therapy after CPR. In-hospital survival rates were 87, 76 and 42%, respectively. Thus, with respect to survival, fibrinolysis may be beneficial in myocardial infarction requiring CPR. However, data are derived from observations, and the differences in survival rates could be the result of selection bias.

Cardiac arrest and confirmed pulmonary embolism

In pulmonary embolism complicated by cardiac arrest successful lysis or fragmentation of an
embolism should logically result in improved circulation, preservation of right ventricular function and improved gas exchange. Recently, a systematic review of case reports and series of patients suffering from confirmed pulmonary embolism complicated by cardiac arrest and treated with lytic therapy before, during or after the arrest, was published. When limited to the 10 existing case series only, with 87 patients included overall, the survival rate ranged from 55 to 100. Although the reported results are good, they are based on uncontrolled cases and very few studies with a higher level of evidence exist. One of these is a retrospective study in which diagnosis, therapy and outcome of patients with cardiac arrest after pulmonary embolism admitted to the emergency department were analysed. In total 1246 patients suffered from witnessed cardiac arrest, 60 had pulmonary embolism of which 18 were established with autopsy. Forty-two patients were diagnosed clinically, of which 21 received rt-PA (11 before CPR) and 21 did not. Return of spontaneous circulation was achieved significantly more often in rt-PA treated patients than those treated without. Survival to hospital discharge was twice as high in the rt-PA group compared with the non-rt-PA group (p = ns, Table 4). In another retrospective study, primarily addressing safety, a proof of concept was shown in 66 patients admitted with cardiac arrest in the course of pulmonary embolism. Both return of spontaneous circulation and survival to discharge were found twice as often in fibrinolytic treated patients (p = ns). These post hoc observations in selected patients suggest that fibrinolysis in case of thrombotic origin of the arrest may be efficacious.

**Cardiac arrest with presumed diagnosis**

From the data described above it becomes clear that fibrinolytic treatment in cardiac arrest might improve neurological outcome and survival after confirmed myocardial infarction or pulmonary embolism. However, the question is whether generalised application of fibrinolytic therapy could also be efficacious in the treatment of cardiac arrest without a confirmed diagnosis, comprising both thrombotic and non-thrombotic aetiologies. Several case reports and case series have been published suggesting potential benefit and acceptable bleeding rates for fibrinolysis during CPR. Recently, several retrospective and prospective studies have been published, also indicating success (Table 5).

The first was a prospective study performed during two consecutive years. In the first year, patients suffering from out-of-hospital cardiac arrest underwent standard CPR. This control-group was compared with patients in the subsequent year who were additionally treated with heparin (5000 U) and rt-PA (50 mg in 2 min) if a return of spontaneous circulation was not achieved within 15 min. In total, 90 patients were included of which 40 received heparin and rt-PA. In the rt-PA group two patients needed blood transfusions because of gastric ulcer bleeding, whereas in the standard

### Table 3

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Design</th>
<th>Initial rhythm</th>
<th>Treatment</th>
<th>Fibroinolysis vs. standard</th>
<th>Survival to discharge fibrinolysis vs. standard</th>
<th>All bleedings fibrinolysis vs. standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Campen</td>
<td>1993</td>
<td>Retrospective</td>
<td>Mainly VF</td>
<td>rt-PA vs. none</td>
<td>33 vs. 36</td>
<td>61% vs. 33%</td>
<td>3% vs. 3%</td>
</tr>
<tr>
<td>Schiele</td>
<td>1996</td>
<td>Retrospective</td>
<td>Mainly VF</td>
<td>rt-PA vs. none</td>
<td>308 vs. 373</td>
<td>52% vs. 38%</td>
<td>NA</td>
</tr>
<tr>
<td>Stewart</td>
<td>1996</td>
<td>Retrospective</td>
<td>Mainly VF</td>
<td>rt-PA vs. none</td>
<td>53 vs. 487</td>
<td>87% vs. 42%</td>
<td>NA</td>
</tr>
</tbody>
</table>

VF, ventricular fibrillation; rt-PA, recombinant tissue plasminogen activator.

### Table 4

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Initial rhythm</th>
<th>Treatment</th>
<th>Fibroinolysis vs. standard</th>
<th>ROSC fibrinolysis vs. standard</th>
<th>Survival to discharge fibrinolysis vs. standard</th>
<th>All bleedings fibrinolysis vs. standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kürkciyan</td>
<td>2000</td>
<td>PEA/asystole</td>
<td>rt-PA</td>
<td>21 vs. 21</td>
<td>81% vs. 43%</td>
<td>10% vs. 5%</td>
<td>14% vs. 0%</td>
</tr>
<tr>
<td>Janata</td>
<td>2003</td>
<td>All</td>
<td>rt-PA</td>
<td>36 vs. 30</td>
<td>67% vs. 43%</td>
<td>19% vs. 7%</td>
<td>25% vs. 10%</td>
</tr>
</tbody>
</table>

ROSC, return of spontaneous circulation; PEA, pulseless electrical activity; rt-PA, recombinant tissue plasminogen activator.
Table 5  

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Design</th>
<th>Initial rhythm</th>
<th>Fibrinolysis vs. standard</th>
<th>ROSC fibrinolysis vs. standard</th>
<th>Survival 24h fibrinolysis vs. standard</th>
<th>Survival to discharge fibrinolysis vs. standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Böttiger</td>
<td>2001</td>
<td>Prospective</td>
<td>All</td>
<td>rt-PA vs. standard</td>
<td>40 vs. 50</td>
<td>68% vs. 44%</td>
<td>15% vs. 6%</td>
</tr>
<tr>
<td>Lederer</td>
<td>2001</td>
<td>Case control</td>
<td>All</td>
<td>rt-PA vs. standard</td>
<td>108 vs. 216</td>
<td>70% vs. 51%</td>
<td>10% vs. 6%</td>
</tr>
<tr>
<td>Stadlbauer</td>
<td>2006</td>
<td>Case control</td>
<td>All</td>
<td>rt-PA/TNK vs. standard</td>
<td>99 vs. 1087</td>
<td>46% vs. 33%</td>
<td>5% vs. 6%</td>
</tr>
<tr>
<td>Fatovich</td>
<td>2004</td>
<td>Placebo control</td>
<td>All</td>
<td>TNK vs. placebo</td>
<td>19 vs. 16</td>
<td>42% vs. 6%</td>
<td>21% vs. 23%</td>
</tr>
<tr>
<td>Abu-Laban</td>
<td>2005</td>
<td>Placebo control</td>
<td>All</td>
<td>t-PA vs. placebo</td>
<td>117 vs. 116</td>
<td>3% vs. 0%</td>
<td>1% vs. 0%</td>
</tr>
<tr>
<td>Rioch</td>
<td>2005</td>
<td>Placebo control</td>
<td>All</td>
<td>rt-PA recombinant tissue plasminogen activator vs. placebo + PEA + pulseless electrical activity</td>
<td>19 vs. 16</td>
<td>42% vs. 6%</td>
<td>21% vs. 23%</td>
</tr>
</tbody>
</table>

In the studies described, all initial rhythms were taken into account. In one trial only patients presenting with pulseless electrical activity without treatment no episodes of bleeding were found, despite prolonged CPR-efforts. Short-term survival was significantly improved: patients who received rt-PA achieved a return of spontaneous circulation more often and were more often admitted to the hospital when compared with controls. Longer term survival, at 24 h and at the time of hospital discharge, was almost twice as high in favour of rt-PA, but this did not reach statistical significance.50 These findings corroborated the findings in a retrospective study of 108 patients receiving rt-PA during CPR and 216 controls. Patients were matched for baseline characteristics, status on arrival and ECG. When compared with controls, fibrinolytic treated patients had a sustained spontaneous circulation significantly more often, were more often alive at 24 h and also more often survived to discharge (p = 0.001, 0.003 and 0.048, respectively).24 The efficacy of fibrinolysis was also suggested in a recent post hoc analysis. In the original study, the effects of vasopressin versus adrenaline were studied in 1186 patients with out-of-hospital cardiac arrest. In total 99 patients additionally received tenecteplase or reteplase, whereas 1087 did not. In this study both short as well as longer term survival were increased, but not significantly: fibrinolytic treated patients were admitted to the hospital more often and discharged alive more often.51 Selection bias could account for this observed potential benefit. First, patients more often had ventricular fibrillation, which is the initial rhythm associated with the highest chance of survival. Second, if patients have ventricular fibrillation myocardial infarction is more likely and fibrinolysis could be more effective. Third, patients were younger, and thus had a better prognosis from the start.

The only randomised double blind placebo controlled trial addressing the efficacy and safety of thrombolysis in patients suffering from out-of-hospital cardiac arrest receiving CPR is the prematurely stopped (due to funding difficulties)TICA trial. Only 35 patients were enrolled: 19 patients received tenecteplase (50 mg bolus) and 16 placebo. Importantly, the mean time to treatment was high: 40 min after onset of the arrest. Return of spontaneous circulation was achieved in 42% of tenecteplase treated patients versus 6% in the placebo-group. However, in the tenecteplase group, patients were significantly younger and more often had ventricular fibrillation as initial rhythm.52 Because of this and the fact the study was stopped prematurely, the data are inconclusive and larger randomised studies are warranted.

In the studies described, all initial rhythms were taken into account. In one trial only patients presenting with pulseless electrical activity without
confirmed diagnosis were analysed. A total of 233 patients with out-of-hospital cardiac arrest with more than 1 min of pulseless electrical activity and unresponsive to initial therapy were randomly assigned to intravenous infusion of t-PA 100 mg or placebo over a 15 min period. One hundred and seventeen patients received t-PA and 116 placebo. Also in this study, time to treatment was high: 35 min. Return of spontaneous circulation was achieved in 21% of t-PA treated patients in comparison with 23% in the placebo-group (p = ns). One patient survived in the t-PA group whereas none in the placebo-group did. From this study, it seems that in cardiac arrest patients with pulseless electrical activity fibrinolysis is not beneficial.53

In summary, the results of most individual studies discussed indicate that in cardiac arrest patients with presumed diagnosis short-term survival is significantly improved, whereas longer term survival is not (Table 5). Although the previously discussed individual studies failed to show improved longer term survival, statistical power was limited and it remains unclear whether one study is sufficient for a definitive conclusion. Nonetheless, in a recent meta-analysis of these studies a significantly improved longer term survival was demonstrated (OR 2.0, 95% CI 1.2—3.3).25 Although promising, publication bias cannot be ruled out completely.

A more definite answer is awaited from the first large scale multicentre randomised, double blind placebo-controlled study, the European TROICA (ThROmbolysis In Cardiac Arrest) trial. Patients presenting with non-traumatic out-of-hospital cardiac arrest receive tenecteplase or placebo. Major inclusion criteria are: witnessed arrest, CPR started within 10 min after onset and continued for a maximum of 10 min, ventricular fibrillation or pulseless electrical activity as initial rhythm and presumed cardiac origin. The primary endpoint is 30-day survival. The secondary endpoints are return of spontaneous circulation, survival at 24 h, survival to discharge and neurological and overall outcome. Also, safety will be assessed by occurrence of intracranial haemorrhage and major bleeding complications. In total 1300 patients were planned to be enrolled.54 Recently, however, the enrolment has been suspended on DSMB advice after inclusion of 1000 patients because of futility. Nevertheless, whereas no difference in the primary endpoint was found, a positive impact of fibrinolysis on neurological outcome or other endpoints is possible. These potential benefits should be weighed against the expected increased risk of bleeding.

Regarding causes for the lack of benefit, one can only speculate. Several factors might contribute. Firstly, non-thrombotic causes of cardiac arrest may represent a larger proportion of the patients than expected. Thus, the incidence of thrombotic causes may have been overestimated in the sometimes rather selected observations on which the trial was designed. Application in a more selected group of patients could provide insight as to whether fibrinolysis might be effective in patients with a higher clinical suspicion of thrombotic cause.

Another explanation may be, that even though the incidence of thrombotic aetiologies may have been as anticipated, the efficacy of fibrinolysis proved to be lower than estimated beforehand, and a potential effect may have been missed due to lack of statistical power. From a logistic point of view, CPR may have been discontinued too early after administration of fibrinolysis, reducing the interval for fibrinolysis to become effective. An alternative explanation may be that the use of heparin during CPR was not allowed. This is in contrast with most previous studies in which heparin was administered alongside fibrinolysis. This may have caused massive thrombin generation after bolus injection of fibrinolysis with subsequent re-occlusion or development of microthrombi damaging the cerebrum. Although in total contradiction with the evidence on which the trial was designed, fibrinolysis may not work at all, or, bleeding complications may have neutralised the benefits.

Clearly, further research is warranted to elucidate the findings of this trial and provide guidelines for clinical practice.

Other reperfusion strategies

PCI in cardiac arrest

In ST-elevation myocardial infarction without cardiac arrest, primary percutaneous coronary intervention has been shown to be very effective in lowering morbidity and mortality.55 Moreover, the risk of bleeding is lower in comparison with fibrinolysis. In cardiac arrest, coronary angioplasty could be an attractive strategy, but data are scarce.

Recently, a retrospective study was conducted addressing the feasibility of percutaneous coronary intervention in cardiac arrest. Forty patients successfully resuscitated from out-of-hospital cardiac arrest caused by ST-elevation myocardial infarction and treated with percutaneous coronary intervention were compared with 325 patients with ST-elevation myocardial infarction without cardiac arrest but also treated with coronary intervention. The 2-year survival in the cardiac arrest-group was as high as 73% versus 93% in the control group.56 In another study, 84 consecutive survivors of
out-of-hospital cardiac arrest with presumed cardiac cause underwent immediate coronary angiography. In-hospital survival for these patients was 38%. With respect to angiographic findings 48% of patients had a total occlusion: in 37 patients angioplasty was attempted and in 28 of these TIMI flow grade 3 was achieved. Another 23% of the patients had one or more stenoses greater than 50% in luminal diameter on angiography. Importantly, the occurrence of pre-arrest chest pain or post-arrest ST-segment elevation had a poor predictive value for occlusion of a coronary artery.10 In any case, both studies show a good outcome and it can be concluded that coronary reperfusion can be successfully achieved with percutaneous coronary intervention, with probably a lower risk of bleeding than fibrinolytic treated patients.

Nonetheless, several remarks should be made. Firstly, at least 90% of patients in both studies presented with ventricular fibrillation. Also, in the first study 90% of patients were already conscious prior to the intervention and patients receiving CPR for more than 10 min were excluded. Because of this and the fact that ventricular fibrillation is the initial rhythm in cardiac arrest patients in only 30—40% in large registries, the incidence of total occlusion in a less selected population will probably be much lower.57 Secondly, cardiac arrest is only in part caused by myocardial infarction. Therefore, coronary interventions can only be beneficial in selected patients with high likelihood of myocardial infarction and is therefore not generally applicable. Thirdly, coronary interventions can only be performed in patients with spontaneous circulation. Fourthly, and most importantly, it will take time before coronary interventions can be initiated because patients with out-of-hospital cardiac arrest have to be transferred and admitted to hospitals with intervention facilities. Finally, experimental support for a beneficial effect of coronary interventions in preventing or dissolving microthrombi in the brain is not available.

Embolectomy in pulmonary embolism complicated by cardiac arrest

Case reports or series on surgical embolectomy in case of massive pulmonary embolism with or without cardiac arrest are few and show a survival rate ranging from 26 to 50%. Only anecdotal reports exist on catheter embolectomy for massive pulmonary embolism. Because of lack of clinical data and the fact that embolectomy can only be performed in specialised centres, both therapies can only be reserved for selected patients.58,59

Conclusion

The evidence available from several observational, mostly non-randomised studies reveals that fibrinolytic therapy has potential as additional treatment during cardiopulmonary resuscitation in patients suffering from non-traumatic out-of-hospital cardiac arrest. Post hoc observations in CPR patients with confirmed acute myocardial infarction or pulmonary embolism provide a proof of concept. Yet, in the acute setting every minute lost in the diagnostic process could result in a marked decrease in prognosis.

Therefore, generalised application of fibrinolysis was tested in cardiac arrest with presumed cause, with a meta-analysis suggesting both increased short- and longer term survival. Besides improved survival, fibrinolysis also seemed to diminish cerebral damage in experimental studies. On the other hand, the risk of bleeding complications is increased by two-fold. Despite the fact the meta-analysis suggests that fibrinolysis is associated with 65 extra episodes of bleeding per 1000 patients treated, of which 17 per 1000 are fatal, there was an overall gain of 79 lives per 1000 treated patients.25 A major disadvantage is the fact that prospective randomised data are scarce and that not all cases of out-of-hospital cardiac arrest will be caused by thrombotic processes. On theoretical grounds, fibrinolysis is not expected to derive much benefit in patients with non-thrombotic causes, except for a putative effect on neurological outcome.

The definite results of the suspended large scale TROICA trial are eagerly awaited for final interpretation, and subgroups of patients might be identified for further research.

For patients with return of spontaneous circulation and admitted to the hospital, reperfusion by angioplasty should be considered as an attractive strategy.

Conflict of interest

None.

References

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