Thrombolysis during cardiopulmonary resuscitation

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Abstract
Numerous experimental researches and clinical observations reveal that immediately after cardiac arrest a significant platelet activation appears which is not counterbalanced by endogenous fibrinolysis and leads to disseminated laying down of fibrin’s concrement in artery and microclots’ formation. The process is being developed during cardiopulmonary resuscitation and extended to a post-resuscitation period. There have been some experimental works and clinical examinations revealing that treatment with heparin and thrombolysis’ application can increase the survival rate after an incident of cardiac arrest. Thrombolysis therapy becomes a new method facilitating prognosis as to patient’s health after cardiac arrest. Presently one can state undoubtedly that either fibrinolysis therapy or thrombolysis therapy is justified at suspicion of an acute pulmonary embolism contributing to patient’s hemodynamic stabilization. In the results it has been obtained hitherto that this sort of therapy, applied during cardiopulmonary resuscitation after prolonged cardiac arrest at acute coronary syndrome increases survival rate and improves patient’s neurological state during a post-resuscitation period. Full confirmation of these observations needs some further multi-centered, randomized studies of the issues under consideration. (Cardiol J 2007; 14: 24–28)

Key words: cardiac arrest, cardiopulmonary resuscitation, thrombolysis

Introduction
Disorders of microcirculation that begin immediately after cardiac arrest and evolve during cardiopulmonary resuscitation are among the most important causes of adverse prognosis of patients after the return of spontaneous circulation. In the postresuscitation period, inefficiency of peripheral perfusion with limited blood volume and impaired heart contractility is caused not only by the lack of adaptation of cardiac output and vascular resistance of pulmonary and systemic circulation but also by coagulation disturbances [1, 2]. Periodic lack of flow causes endothelial dysfunction and activation of homeostasis resulting in platelet clots and thrombus formation which in turn cause abrupt occlusion of many small vessels. Thus organ perfusion is not preserved in spite of correct values of systemic hemodynamic parameters (“no-reflow phenomenon”) [3]. The most important endpoint of resuscitation is the return of proper function of central nervous system, otherwise preservation of other organ function is only secondary [4].

Searching for methods which increase the efficacy of resuscitation procedures is an important direction of scientific studies. These are aimed at potential improvement of tissue perfusion during resuscitation and limitation of results of reperfusion after the return of spontaneous circulation. Apart from moderate hypothermia, currently there is no available method substantially improving neurological status after cardiac arrest [5]. The effects of thrombolysis are very promising [6, 7]. Thrombolytic
therapy during resuscitation is aimed at restoration of flow in the vessels of coronary or pulmonary circulation, occlusion of which could lead to cardiac arrest, but at the same time it helps to prevent formation of many small thrombi in the vessels of important organs.

Experimental studies and clinical trials to date have demonstrated that consequences of coagulation disturbances emerging immediately after cardiac arrest could be reversible with thrombolytic therapy, if it was started immediately. Because currently there is no absolute contraindication for such therapy, the decision of its initiation should be based on evaluation of potential benefit in each individual case.

**Coagulation disturbances and their consequences during periresuscitation period**

The coagulation and fibrinolysis processes are influenced by many general and local conditions, related to flow regulation, and later reperfusion, including hypoxemia, ischemia, catecholamine and free radicals release.

In experimental and clinical studies major coagulation disturbances emerging during cardiac arrest were demonstrated [8]. Disseminated intravascular coagulation with thrombi formation and fibrin deposition in microcirculation leads to multi-organ damage [9].

In the experimental model, directly after cardiac arrest and later during resuscitation procedures, activation of coagulation was observed, involving exogenous as well as endogenous pathway. Its consequence is microthrombosis of capillaries in the brain, lungs and kidneys [10]. In animal studies, multiple microthrombi in brain vessels and disseminated intravascular coagulation were demonstrated as early as 5 min from cardiac arrest into cardiopulmonary resuscitation. Clots were observed in large arteries after 20 min from the return of spontaneous circulation in normothermy and after 40 min, when cardiac arrest was induced in hypothermic conditions [11]. Gross and microscopic specimen of brain vessels showed the presence of clots shortly after cardiac arrest. It was proved that activation of coagulation and platelets not only intensify early disorders of brain perfusion and “no-reflow” phenomenon, but also cause late hypoperfusion [12].

The first paper which demonstrated sudden activation of coagulation during postresuscitation period in humans was published in 1995 [9]. The significant activation of coagulation leading to trombin formation (with increasing concentration of soluble fibrin monomers that indicates systemic, not only local creation) was observed in patients undergoing cardiopulmonary resuscitation and after return of spontaneous circulation. Activation of plasma coagulation factors and platelets in the postresuscitation period observed in clinical conditions was significant and resulted in fibrin deposition and microthrombi developing in the vessels [9]. It is known, that concentration of white blood cells and intravascular coagulation triggered with platelet aggregation may lead to microcirculation disorders [13, 14].

Conversion of fibrinogen to fibrin leads to increase of plasma thrombin — antithrombin (TAT) complex in patients after cardiac arrest. Significant increase of TAT concentration is followed by a decrease of anticoagulant factors like active S and C proteins [8]. Activation of C protein warrants natural balance, physiologically suppressing activation of coagulation and inflammatory reaction. In clinical studies increased, endogenous activation of C protein was observed only in very short period after out of hospital cardiac arrest. Although fibrin creation and sudden endothelial stimulation in the early periresuscitation period initially facilitate activation of C protein, maintaining this process is complicated by progressively developing endothelial dysfunction [15]. Based on experimental model of ischemic brain and spinal cord damage it was proved that exogenous active C protein may minimize results of ischemic and postreperfusion damage in the nervous system [16].

Increased activity of tissue plasminogen activator which was demonstrated directly after return of spontaneous circulation decrease during next 24 h and is practically irrelevant, while the activity of inhibitor of plasminogen activator is significantly increased and in consequence leads to progressive unlimited trombin generation. Also during later postresuscitation period, despite progressive intravascular coagulation, still no increase of concentration of the coagulation inhibitors is observed [17]. Thus the majority of patients develop inhibition of fibrinolysis, which is physiologically accompanied by coagulation. It can be due to increasing concentration of PAI-1, which increases even more during early postresuscitation period [17].

These data confirm activation of coagulation during postresuscitation period, with activation of endogenous fibrinolysis accompanying only in the early period after cardiac arrest. This leads to haemostatic disequilibrium, and, in consequence, to microthrombosis and microcirculation disorders [18].
Significant activation of platelet aggregation without simultaneous activation of prostaglandin I and F synthesis during periresuscitation period, not sufficiently balanced by endogenous fibrinolysis, is an additional factor of uncontrolled blood coagulation [13].

**Effects of thrombolytic therapy during cardiac arrest caused by acute coronary syndrome or massive pulmonary embolism**

Acute pulmonary embolism or myocardial infarction are the cause of cardiac arrest in 50–70% of patients. Thrombolytic therapy during acute coronary syndrome is an alternative to percutaneous coronary angioplasty. Prompt admission allows for early opening and maintenance off low in the culprit artery. In the group of 681 resuscitated patients after cardiac arrest during myocardial infarction, in 308 fibrinolysis was administered, resulting in lower in-hospital mortality (48% vs. 62%) [19]. Other studies of patients after cardiac arrest related to myocardial infarction treated with thrombolysis demonstrated better prognosis without excess major bleeding complications [20].

Pulmonary embolism is common in hospitalized patients with mortality rate of only 0.4% [21]. But massive pulmonary embolism is the second most often cause of nontraumatic cardiac arrest. In 45–90% of patients who died of pulmonary embolism, cardiac arrest occurred after 1–2 h from symptom onset [21]. Experience indicates that classic cardiopulmonary resuscitation in such cases is rarely successful without treatment like pulmonary embolectomy or thrombolysis administered early. Immediate pulmonary embolectomy is not possible in most cases because of logistic reasons. Alternative therapy, available even in out-of-hospital conditions, is thrombolysis [22]. According to some authors pulmonary embolism as a presumed cause of cardiac arrest is an agreed indication for thrombolytic agent administration. It should be underlined that possible misdiagnosis of myocardial infarction when pulmonary embolism was the cause did not worsen the prognosis if thrombolytic agents were administered [22].

**Estimation of effects of thrombolytic therapy during out-of-hospital nontraumatic cardiac arrest**

Numerous case reports or studies including small number of patients indicate that thrombolytic therapy used as ultima ratio (when the only other possible solution would be termination of cardio-pulmonary resuscitation) improves outcome in the group of resuscitated patients [23]. Evidence for efficacy of out-of-hospital thrombolysis justify attempting such therapy in patients with out-of-hospital nontraumatic cardiac arrest of unknown etiology. There are numerous case reports pointing to increasing success rate of cardiopulmonary resuscitation by additional administration of fibrinolytic or thrombolytic therapy [23]. First study which proved efficacy of thrombolytic therapy in a patients with prolonged cardiopulmonary resuscitation performed after out-of-hospital cardiac arrest was published only in 2001 [24]. It included 90 patients after cardiac arrest probably related to myocardial infarction or pulmonary embolism without contraindication to thrombolytic therapy. In case 15 min standard cardiopulmonary resuscitation was ineffective, 50 mg rt-PA and 5000 U of unfractioned heparin were administered. If there was no return of spontaneous circulation after next 30 min, the doses of the drugs were repeated. In 40 patients in whom thrombolytic therapy was administered, the return of spontaneous circulation was achieved in 68% (vs. 48% in the group not treated with rt-PA). Thirty five percent of patients survived first 24 h, compared to 22% in the group not treated with rt-PA, and 15% of patients receiving rt-PA were discharged from hospital (vs. 8% in group without rt-PA). There were no major bleeding complications related directly to cardiopulmonary resuscitation [24].

Another large prospective study included 233 patients with pulseless electrical activity (PEA) cardiac arrest [25]. During cardiopulmonary resuscitation, standard cardiopulmonary resuscitation was used with or without additional 15-min infusion of 10 mg rt-PA. In contrast to other studies performed so far, this study did not show beneficial effect in the rt-PA group (21.4%) over placebo (23.3%) [25]. But this study was vividly criticized because of methodological defects [26]. Interesting results were obtained in a large group of 13000 patients with myocardial infarction. Two subgroups were compared: one group of 303 patients after cardiac arrest who did not receive thrombolysis during cardiopulmonary resuscitation and another group of 67 patients who had received thrombolysis after the return of spontaneous circulation [27]. It was proved that cerebral damage during periresuscitation period occurs only in 9% patient treated with thrombolytic agents compared to 40% of untreated patients [27].

In clinical studies to date no significant increase in frequency of major bleeding complications after administration of thrombolytic therapy in patients
during cardiac arrest was found [23]. Analysis of all published papers evaluating effects of fibrinolysis during cardiopulmonary resuscitation did not point to increased risk of bleeding complications compared to standard therapy [7]. Moreover, good neurological status of patients receiving thrombolysis was emphasized [6, 28]. There was no increased frequency of other complications like rupture of aortic aneurysma, cardiac tamponade or pleural hematoma [29]. Several authors suggest that in some situations with no alternative treatment, when standard resuscitation is unsuccessful, possible contraindications to fibrinolysis/thrombolysis should be treated as relative or even ignored in individual cases [6].

Thrombolytic therapy which is accepted in patients with cardiac arrest related to pulmonary embolism or myocardial infarction is not regarded as standard during cardiopulmonary resuscitation [30]. The main reason is not the lack of efficacy of such therapy in nontraumatic cardiac arrest but fear of bleeding complications that may follow, related to drug properties and mechanical injuries resulting from cardiopulmonary resuscitation. Growing number of reports concerning safety of thrombolytic therapy during cardiopulmonary resuscitation in patients with massive pulmonary embolism and myocardial infarction show beneficial effect on hemodynamic stabilization after restoration of spontaneous circulation and improved prognosis, suggesting serious consideration of such treatment in every case of nontraumatic cardiac arrest. Despite available evidence suggesting beneficial effect of thrombolytic therapy during cardiopulmonary resuscitation it can not be unambiguously stated whether the benefit relates to higher survival rate only or to improvement of neurological status as well (what was demonstrated in experimental and clinical works to date) [6, 28]. Hence, much hope is elicited in relation to forthcoming results of a large prospective, multicenter, randomized and controlled trial estimating efficacy and safety administration of thrombolytic therapy during cardiopulmonary resuscitation — TROICA (Thrombolysis In Cardiac Arrest).

References

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