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REVIEW

Thrombolysis and cardiac arrest

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Abstract: Cardiac arrest (CA) is a serious clinical condition that might be responsible in many cases for death, in other at least for development of irreversible multiple organ dysfunctions. During and after the CA a significant coagulopathy develops causing a decrease in proper tissue perfusion even if an early return of spontaneous circulation (ROSC) is achieved (no-reflow phenomenon). Administration of thrombolytics can solve the problem by destructing the blood clot in both macrocirculation and microcirculation. Results of some clinical trials proving an effectiveness of thrombolysis were published in the literature. Generally, it was done by describing its positive influence on some important clinical outcome measures (24hour survival, number of hospital admissions, better neurological status etc.) without significant increase in the number of bleeding complications. However, recent pivotal evidence based medicine (EBM) trial represented by TROICA study did not confirm the expected positive results. Because of that and also for other reasons (cost, fear of adverse effects, little practice etc.) thrombolysis, although theoretically promising therapeutical intervention, is not overly recommended and used in routine clinical practice in both out-of-hospital and in-hospital settings *(Fig. 2, Tab. 4, Ref. 24).* Full Text in free PDF *www.bmj.sk.*
Key words: thrombolysis, cardiac arrest, fibrinolysis, coagulation, cardiopulmonary resuscitation, TROICA, plasminogen activators, thrombolytics.

Abbreviations: ACS – acute coronary syndrome, AMI – acute myocardial infarction, AT – antithrombin, CA – cardiac arrest, CPR – cardio pulmonary resuscitation, FDPs – fibrin degradation products, ILCOR – International Liaison Committee on Resuscitation, MODS – multiple organ dysfunction syndrome, MPE – massive pulmonary embolism, NSTEMI – non-ST segment elevation myocardial infarction, PAI-1+2 – plasminogen activator inhibitor 1 + 2, PC/PS – protein C/protein S complex, ROSC – return of spontaneous circulation, STEMI – ST segment elevation myocardial infarction, TAFI – thrombin-activatable fibrinolysis inhibitor, plasma carboxypeptidase B2, T-AT – thrombin-antithrombin complex, TF – tissue factor, TFPI – tissue factor pathway inhibitor, tPA – tissue plasminogen activator, UFH – unfractioned heparin

Introduction (epidemiology and review's purpose)

Cardiac arrest has so far regrettably very poor prognosis. There are many pathologic conditions that might be responsible for developing this significant life-threatening clinical situation. From out-of-hospital as well as in-hospital point of view, the two most frequent reasons for CA are acute myocardial infarction (AMI) and massive pulmonary embolism (MPE). The mentioned clinical conditions are caused pathophysiologically by a clot occlusion of a blood vessel (artery) followed by significant decrease or even interruption of the blood flow into the specific part or sometimes the whole organ (heart, lungs). This usually causes severe impairment of tissue oxygen supply and might also consequently cause a serious loss of physiologic organ function or even a global systemic circulatory arrest. Therefore, rapid administration of clot dissolving treatment is sometimes vital.

CA can be described as a complete and abrupt fade-away of systemic circulation because of the failure of normal systolic myocardial contraction (ineffective function of myocardial pump). In emergent conditions, this diagnosis, as a gold standard, can be made by an absence of carotid artery pulse detected by palpation (24) and it is reserved, in particular, for experienced healthcare professionals. Afterwards, the definitive diagnosis is established by ECG. Apart from the basic etiologic reasons (Tab. 1) there four types of the most serious cardiac arrhythmias such as ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), asystolia and pulseless electrical activity (PEA) also known as electromechanical dissociation can be involved in the etiology. The above mentioned most frequent causes of AMI and MPE are the main reason for CA in 50–70 % of all cases (1, 2, 7).

Thrombolysis, as a direct way for effective destruction of the blood clot, might be considered a promising component of the treatment of the patients with CA (1, 2). Therefore, the main goal of the review is to describe the pathophysiology of CA on the level of both macrocirculation and microcirculation, the theo-

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Causes of cardiac arrest	
acute forms of ischemic heart disease (ACS)	unstable angina
	AMI (STEMI, NSTEMI)
mechanical	MPE
	pericardial tamponade
	valvular disease
	tension pneumothorax
metabolic	hypokalemia, hyperkalemia
	hypomagnesemia, hypermagnesemia
	kalcemia
	hypophosfatemia
	hypoglykemia, hyperglykemia
hypoxemia, asfyxia	
trauma – hypovolemia, exsanguinatio	
acid-base abnormalities	
toxigology (drugs, poisoning)	
hypotermia	

retical principle of thrombolysis and its potential role in resolving any of the clinical conditions following CA. Finally, results and summary of up to date available literature will be presented.

Patophysiology of coagulopathy due to cardiac arrest

At first, trying to better understand the therapeutic intention of using thrombolytics during CPR, one important question arises: What does really happen inside systemic blood vessels during and after CA?

Preserving blood fluidity and as well simultaneously properly working clotting system are one of the basic conditions for maintaining homeostasis and hemodynamic stability. Blood fluidity is one of the most important requirements for delivering necessary amount of oxygen and nutrients to the tissue cells and by doing this to preserve proper organ function. For that purpose, some vital humoral and cellular functions are available including: maintained sufficient blood flow and viscosity, properly functioning platelets, coagulation factors, inhibitors, components of the fibrinolytic system, intact layer of endothelial cells together with its sub-endothelial space including, among others, also some important structural proteins and functioning vascular smooth muscles.

All basic phases of hemostasis (1. primary hemostasis related mainly to platelets, 2. secondary hemostasis related to intravascular coagulation factors and 3. fibrinolysis) are intricately regulated and extremely complex processes. Generally, hemostasis depends on the interaction between competent cells, structural proteins and some relevant humoral factors.

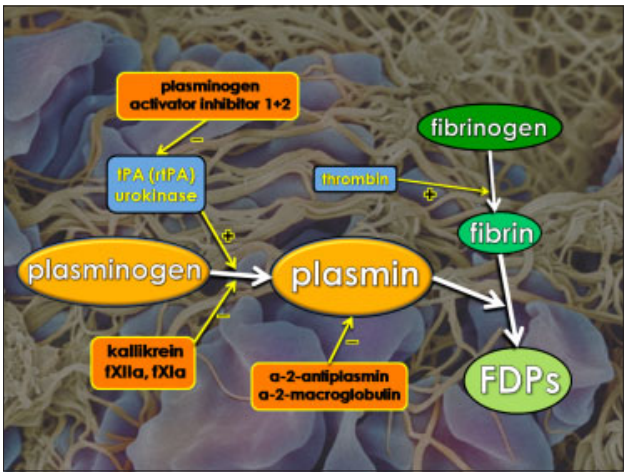

Fig. 1. Conversion of plasminogen into plasmin, fibrinolysis and some related influencing factors (inhibitors and activators).

In the first phase of hemostasis, an important role is played by platelets and endothelial cells with their distinct bioactive products (thromboxan – TXA_2, platelet activating factor – PAF4, ADP etc.), tissue-factor-bearing microvesicles and specific membrane receptors formed mostly on protein basis (thrombomodulin etc.) which usually also exist and might be detected in soluble form. No less significant are sub-endothelial structural protein molecules (fibronectin, collagen, vitronectin, laminin etc.) and humoral factors (thrombin, heparin-like substances, von Willebrand factor – vWf, ect.).

In the 2nd phase (intravascular blood coagulation) there is intricately and perpetually sustained balance between pro-coagulant (serine proteases, platelet membrane phospholipids, Ca^{2+}, soluble TF etc.) and anticoagulant (antithrombin - AT, protein C/protein S, tissue factor pathway inhibitor – TFPI, urokinase, heparin-like substances etc.) blood factors.

During the 3rd process of hemostasis (fibrinolysis) (Fig. 1) many different enzymes, serum proteins and cell products with regulatory and contra regulatory functions (plasminogen, tissue plasminogen activator – tPA, plasminogen activator inhibitor – PAI-1+2, á-2-antiplasmin, á-2-macroglobulin, FDPs, thrombin-activatable fibrinolysis inhibitor – TAFI etc) are present a play an important role.

During CA the effective circulation stops. That roughly means that blood does not sufficiently move inside vessels in both, macrocirculation as well as microcirculation. If ROSC is not immediately achieved then after a short time interval (approximately 4 – 5 minutes) when locally available oxygen content is consumed, several pathophysiologic processes begin. The most important include development of platelets and endothelium activation and in most severe and/or prolonged cases also progressive endothelial dysfunction. Activated platelets aggregates create clumps in microcirculation and also undergo so-called “flip-flop” reaction, where phosphatidilserine is exposed on the outer membrane leaflet. Phosphatidylserine provides the surface for the assembly of coagulant enzyme complexes which generate

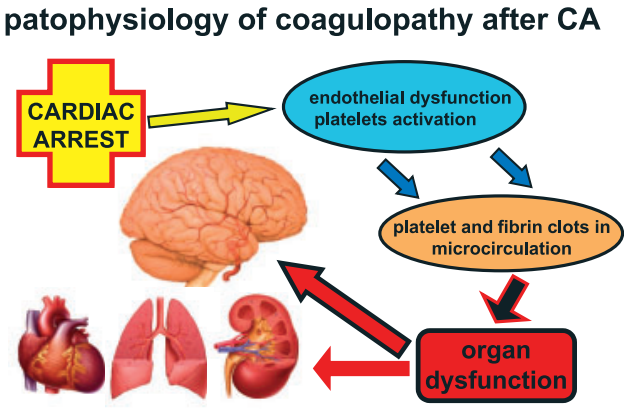

Fig. 2. Pathophysiology of microcirculatory dysfunction of vital organs after CA.

thrombin and enable fibrin deposition under the picture of systemic activation of coagulation (1, 2) which is not sufficiently counterbalanced by properly activated endogenous fibrinolytic system (3). This processes continue despite the initiation of cardiopulmonary resuscitation and usually even after eventually achieved ROSC. Thus, there is a risk of continuation of organ tissue perfusion impairment even if adequate systemic hemodynamic parameters are relatively quickly reached and maintained. This situation is commonly called no-reflow phenomenon (1, 2, 5, 6).

The most important and vulnerable organ to hypoperfusion is central nervous system. In hypoxemic state developed significant functional and structural changes are usually irreversible. Indeed, also microcirculation of other organs is often affected and their normal function might be also significantly compromised (kidneys, heart, lungs etc.) (Fig. 2) and this could lead to the clinical picture of multiple organ dysfunction syndrome/multiple organ failure (MODS/MOF) (2).

The histopathologic structure of arterial thrombi is consistent with this model, but the sequence of events leading to venous thrombosis is less clear. Some evidences indicate that stasis can result in hemoglobin desaturation leading to a hypoxic insult to the endothelium. The endothelium is primarily oxygenated and fed directly by the blood perfusing the vessel lumen. Hypoxia can cause cellular responses that range from no effect at all, to cell activation, dysfunction, hibernation, and even to cell death, depending on the degree and duration of the hypoxia. Endothelial P-selectin expression in ischemia is essential for leukocyte infiltration of the vessel wall and target tissue and, for that matter, for the binding of tissue-factor-bearing microvesicles to initiate coagulation and thrombosis (22, 23).

In the macrocirculation the blood clotting occured approximately after 20 minutes in normotermic patients and after 40 minutes in hypothermic patients (2). Aside of the main topic of the article this fact might demonstrate one of the positive effects of spontaneously or artificially developed hypothermia during CA.

The persisting systemic activation of intravascular coagulation system and concomitant inhibition of fibrinolysis could be (after ROSC) detected in blood serum by elevated levels of soluble fibrin monomers (sm-fibrin), thrombin antithrombin complex (T-AT), PAI-1 and finally also decreased activity of protein C/protein S (PC/PS) complex. Moreover, often long-lasting elevated blood level of PAI-1, in context with impaired fibrinolysis, is sometimes considered responsible for late organ hypoperfusion (2, 7) even hours from CA.

Role of thrombolysis (rationale)

Intravascular obstruction by blood clot, no matter what type of vessel is affected, can be resolved by several treatment strategies. Aside from recently mostly used direct angiologic intervention, which is usually considered to be the best option for many patients, there is also available a bit older conservative approach with the help of highly effective drugs as causal or preventive medication. Importance of such therapeutic approach is especially highlighted in situations, when radical angiologic intervention is contraindicated or not available in due time. There are several drug groups affecting hemostasis in the sense of inhibition or activation of a certain component in a certain phase of the coagulation process to generate state of therapeutic hypocoagulation. They are collectively called antithrombotic (Tab. 2).

At first place there are drugs generally called antiplatelet drugs affecting primary hemostasis (platelet activation and aggregation) by several specific mechanisms. However, description of these substances goes beyond the frame of this article.

antithrombotics			
1. antiplatelet drugs	cyclooxygenase (COX) enzyme inhibitors	salicylates	
	adenosine reuptake inhibitors	dypiridamol	
	ADP receptors inhibitors	clopidogrel, ticlopidin	
	cAMP phosphodiesterase inhibitor	cilostazol	
	glycoprotein IIb/IIIa inhibitors	abciximab, eptifibatide, tirofiban	
	prostaglandin analogue, prostacyclin, PGI_2	epoprostenol	
2. anticoagulants	vitamin K antagonists (inhibition of maturation of fII, fVII, fIX, fX, PC, PS PIVKA-protein induced by vitamin K absence)	warfarin, dikumarol, ethyl biscoumacetate	
	factor Xa antagonists (+ anti fII effect)	UFH - heparin	
		LMWH	bemiparin, certoparin, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, tinzaparin
		heparinoid	danaparoid, sulodexide, dermatan sulfate
		direct Xa inhibitors	xabans: rivaroxaban
	direct fII antagonists	bivalent: hirudin	
		univalent: argatroban, dabigatran, melagatran	
	other	defibrotide, ramatroban, antithrombin III, drotrecogin alfa	
3. fibrinolytics (viz tab 3)			
4. other	citrate, EDTA, oxalate		

thrombolytic agents		
streptokinase	STK	Streptase, Kabikinase
urokinase	urokinase-type plasminogen activator (uPA)	Rheotromb, Abbokinase
alteplase	tissue plasminigen activator (tPA), plasminogen activator, tissue (PLAT)	Actilyse, Activase
reteplase	non-glycosylated form of human tPA	Retavase, Rapilysin
tenecteplase	TNK	Metalyse, TNKase
anistreplase	anisoylated plasminogen streptokinase activator complex (APSAC)	Eminase
saruplase		
brinase		
ankrod		Arwin
APC (drotecogin alpha)	rhAPC -recombinant activated protein C	Xigris
protein C		Ceprotin
other agents: **alfimeprase, pamiteplase, silteplase, nateplase, tisokinase, monteplase, duteplase, nasaruplase**		

The second group, often used during the last years, includes typical anticoagulant agents such as heparin or, as more recent and better option, substances as low molecular weight heparins (LMWH) and xabans (rivaroxaban) with decreased risk of adverse effects and more user- and patient-friendly pharmacological characteristics. These drugs are able to effectively stop the growth and spreading of the blood clot and concurrently allow natural dissolution of the clot by innate fibrinolytic substances.

The next group of drugs, and from the point of view of this article fundamental, is thrombolytics (also called fibrinolytics). Their main pharmacologic effect is conversion of plasminogen to plasmin or, in new preparations, additionally direct cleavage of fibrin. Serum protein plasminogen itself has not the ability to cleave fibrin strands but binds to it. After binding to the fibrin some fibrinolytics are able to convert plasminogen to plasmin. Plasmin then cleaves fibrin and that way provides dissolution of the clot and FDPs production. Fibrinolytics might be divided into two groups related to their ability to affect both free and fibrin-bound plasminogen or just fibrin-bound plasminogen (1. nonspecific first generation – streptokinase and 2. specific - tPA). There are several commercially available thrombolytic agents nowadays for use and also several new ones involved in research. The newest ones have additional ability to directly cleave fibrin, such as alfimeprase (Tab. 3) (9).

Generally, thrombolytics could be used either intravenously (non directed systemic thrombolysis) or intraarterially (directed local thrombolysis). In clinical setting they are often administered together with classic anticoagulants (UFH, LMWH). The oldest ones (STK and UK) are at present almost eradicated from regular practice. It is mainly for their risks and adverse effects. The most used and important thrombolytic during last years is rtPA – alteplase (Actilyse) and more recently tenecteplase (TNKase) with advantage such as patient's body-weight adjustable dosage.

The very basal requirement and necessary condition for effective thrombolytic action is to bring sufficient amount of the medication to the close proximity and also into the blood clot. Some authors call this process blow flow (6). To provide it or to increase its probability, there is a need for precise and well-performed mechanical part of cardiopulmonary resuscitation (chest compressions) as well as the quickest possible administration of the drugs.

What do we actually want to achieve by using thrombolytics during CA?

Firstly, the most important intention is highly targeted treatment of the primary cause of the illness on the very site of the problem (AMI – occlusion of coronary arteries, MPE – obstruction of pulmonary artery). Secondly, thrombolytics dissolve by that time already created blood clots in microcirculation. This might be the basal condition to reverse no-reflow to reflow phenomenon and to improve patient's overall outcome. It especially applies to the most fragile oxygen-supply dependent nervous tissue and thus influences the extremely important clinical outcome: the neurological status (11).

Possible adverse effects of thrombolysis

Some significant risks following the use of thrombolytics should be taken in account. First generation (streptokinase) is at present considered obsolete for their immunologic adverse reactions (anaphylaxis, immune complex disease), hypotension, likelihood of myocardial rupture and significant reperfusion injury (cardiac arrhythmias) (1, 20). Moreover, the unspecific activity against free plasminogen results in significant increase of risk of severe bleeding complications. Nowadays the most used recombinant tissue plasminogen activators (alteplase, tenecteplase) are quite safe according to aforementioned immunologic adverse effects, but they brought with them also the risk of significant bleeding complications. The fear of bleeding is one of the main reasons why many physicians hesitate to use thrombolytics in clinical cases when indication is evident.

In relation to using thrombolysis during CPR two groups of the most frequent bleeding complications can be described. They could be divided according to direct connection to the mechanical component of CPR (Tab. 4).

Majority of to date published trials frequently address this sort of threatening adverse effects. Actually, the overall results of the trials are quite promising. No significant increase in bleed-

bleeding complications during thrombolysis	
within the contex of CPR	without the contex of CPR
Cardiac tamponade	intracecebral haemorrhage, encephalorhagia
pleural haematoma, haemothorax	gastric or duodenal ulcer haemorrhage
rupture of aneurysm of thoracic aorta	intestinal haemorrhage
chest wall subcutaneous haematomas	

ing complications in both aforementioned groups and also in out-of-hospital and in-hospital setting during or after administration of thrombolytics during CPR were found compared to administration of thrombolytics alone or compared to CPR alone (1, 21).

In conclusion, it is obvious that the benefits following thrombolysis considerably outweigh possible risks. Therefore, the treatment could be considered sufficiently safe and thrombolytics have no longer contraindication for use during the CPR (24).

Published clinical trials

Many of to date published small studies suggest promising results such as increased number of ROSC, increased number of hospital admissions and improved long-term survival compared to patients group receiving standard treatment (1, 13, 14, 15, 16). Some of them also showed faster and longer-lasting hemodynamic stabilization (12, 18) and also better neurological outcome in patients who survived and was eventually released from hospital (16, 17, 18). Results related to short and long term survival are, however, quite heterogeneous (24-hours survival, 30-day survival, survival to the date of hospital discharge), but most studies if not proved then at least described positive trends in survival outcomes (15, 16). Safety assessment considered the most important adverse effect – the risk of bleeding complications, statistically insignificant (19).

Most of the papers naturally divided patients according to time of drug administration into in-hospital and out-of-hospital studies. However, apart from aforementioned promising results the clinical trials published until 2005 are quite sparse and often burdened with some methodological problems. For example sometimes there are different inclusion criteria (PEA as first emergency diagnosis (4) versus witnessed CA), small groups of patients (sometimes even just case reports), non-randomized character, and different used thrombolytics. Moreover, there were often inappropriate dosing and indistinct time intervals of drug administration and unclear metabolic a biochemical status (6) as well as not mentioned possible effect of antecedent artificial of innate coagulation disturbances and concomitant drug interactions. Therefore, in compliance with evidence based medicine requirements, there was an apparent need for large, multicenter, randomized study to prove efficacy and safety of thrombolysis. The main intention was to produce unambiguous and solid clinically relevant results and create overly accepted recommendations.

Therefore main emphasis was put into randomized, double blind, placebo-controlled, multicenter clinical trial started in 2005, the TROICA study (7). The study was in principle, based on administration of tenecteplase in out-of-hospital setting in patients suffering from witnessed CA of presumed cardiac origin. Almost every important author publishing on the topic participated in this trial and the results were highly anticipated. Every important clinical and safety endpoints were included into study observation. It was planned to enroll 1300 patients to have sufficient statistical power. However, after preliminary interim analysis, the study was stopped after enrollment of 1050 patients, because comparing study and control group there was no positive trend in results in all main endpoints. An attempt to explain the failure was based on fact that patients with quick ROSC were not included for randomization; moreover patients with prolonged CPR were enrolled, which could mean less sufficient penetration of drug to close proximity and into the blood clot. Moreover possible adverse interactions and malfunction of tenecteplase in cases of certain pathophysiologic conditions commonly expected after CA (metabolic acidosis, hyperglycemia, presence of free radicals, influence of concomitantly administered of vasoactive therapy etc.) were not taken into account (2, 5, 6, 7).

Nonetheless, apart from possible explanations of the failure, results of TROICA study were generally unfavorable. No beneficial effect of thrombolysis compared to placebo was showed, so one of the main conclusions was that thrombolysis could not be nowadays recommended for routine use in patients suffering CA with prolonged CPR. But it was also suggested that despite of negative results of TROICA study, the effort to eradicate possible flaws should not be discontinued. Further research is warranted and needed.

Conclusion

Use of thrombolytics in the setting of CPR appears to be overly promising. This is either from theoretical pathophysiological point of view or due to growing amount of evidences presented in many clinical trials. However, to date the most important large randomized study TROICA did not show any significant difference in various observed essential indicators of clinical outcome. Despite the possible explanation of these clinical results, authorities do not presently recommend routine administration of thrombolytics to the patients undergoing prolonged CPR. Significant spread of the therapy into basic practice in out-of-hospital and in-hospital care is also hindered by the high cost and fear of potential adverse effect of the medication. On the other side, there is no absolute contraindication for the therapy, thus every physician at the scene of out-of-hospital CA of presumed non-traumatic cardiac etiology, and therefore in need to make an immediate decision, should consider the use of thrombolytics and weighed its potential benefits and drawbacks individually case by case.

Actually, in out-of-hospital settings medical staff of Emergency Care units in our region is not using thrombolytics during the CPR. It is in concordance with in-hospital practice where physicians of Emergency and Coronary ICU's use thrombolytic therapy only in severe cases of hemodynamic instability in patients suffering MPE irrespective to the need of CPR following CA.

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