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Role of thrombolysis in cardiac arrest

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Introduction

Fulminant pulmonary embolism (FPE) and acute myocardial infarction (AMI) are responsible for a large number of cardiorespiratory arrests that have an extraordinarily high mortality rate despite correct application of cardiopulmonary resuscitation (CPR). Thrombolysis has proven very efficacious in AMI, reducing the infarct size and the mortality [1], and also beneficial for the FPE that courses with any type of instability [2]. It might be assumed that thrombolysis is indicated both during or after CPR for the most severe patients who most need it, i.e. patients with AMI or FPE who suffer cardiac arrest. However, the usual CPR maneuvers can produce serious complications, especially hemorrhagic ones, that can be exacerbated with thrombolytic therapy. Many authors [3] and scientific societies [4, 5] have absolutely or relatively advised against thrombolysis during or after CPR, although this prescription was not

based on scientific evidence. Indeed, most studies on the efficacy of thrombolysis excluded patients who had undergone CPR [6].

Many cases and case series, however, have reported the successful application of thrombolysis as an advantageous measure during or after CPR. Recent studies have evaluated the safety and efficacy of thrombolysis in patients who suffered cardiac arrest due to FPE [7, 8].

Böttiger BW, Bohrer H, Bach A, Motsch J, Martin E (1994) Bolus injection of thrombolytic agents during cardiopulmonary resuscitation for massive pulmonary embolism. Resuscitation 28:45–54

This excellent paper by Böttiger et al. [7] reviewed all of the published studies on the administration of thrombolysis in patients with FPE who require CPR maneuvers. Unfortunately, controlled studies or works that of-

ferred high-grade evidence were not found and only case studies and case series were reported, generally in German and from central Europe. Although these studies had a very low level of scientific evidence, they all showed beneficial results and described survival rates of over 50%, leading the authors of the review to conclude that thrombolytic therapy may help to reduce mortality in this setting. Furthermore, the studies reviewed showed no apparent increase in fatal hemorrhagic complications, so that Böttiger et al. recommended the utilization of this approach in patients with FPE requiring CPR maneuvers.

Kürkciyan I, Meron G, Sterz F, Janata K, Domanovits H, Holzer M, et al. (2000) Pulmonary embolism as cause of cardiac arrest: presentation and outcome. Arch Intern Med 160:1529–1535

More recently, Kürkciyan et al. [8] retrospectively studied 60 patients who suffered cardiac arrest as a result of FPE. Pulmonary embolism was initially suspected as the cause of the arrest in 42 of these patients and this diagnosis was subsequently confirmed. Out of these 42 patients, 21 received systemic thrombolysis with 100 mg alteplase during ongoing CPR ($n = 11$) or shortly before ($n = 4$) or after ($n = 6$) cardiac arrest. There were hemorrhagic complications in this group, but no death was attributed to them. Two patients survived to hospital discharge, whereas, only one patient among the 21 patients treated without thrombolysis survived to that point. During the CPR maneuvers, a return of spontaneous circulation was achieved in 17 patients (80.95%) of the group treated with thrombolysis compared with only 7 patients (33.33%) of the group treated without it ($p = 0.03$). The high global mortality could be explained, at least in part, by the fact that over half of these patients suffered prolonged cardiac arrest, with most dying from untreatable shock or severe cerebral damage. Although this study was retrospective and showed no significant difference in mortality between the two groups, it is of interest that a return of spontaneous circulation was more frequently achieved in the patients treated with thrombolysis, because this could be expected to induce a reduction in the mortality from cardiac arrest. Furthermore, in over two-thirds (42/60) of the patients studied the diagnosis of FPE was correctly established on the basis of simple clinical suspicion, suggesting that clinical suspicion of FPE may be adequate to indicate the administration of thrombolysis for cardiac arrest.

The role of thrombolysis has not only been studied in the setting of FPE that requires CPR maneuvers. There are also a few studies that evaluate the safety and efficacy of thrombolysis in patients who suffered cardiac arrest due to AMI [9, 10, 11, 12, 13, 14].

Van Campen LC, Van Leeuwen GR, Verheugt FW (1994) Safety and efficacy of thrombolysis for acute myocardial infarction in patients with prolonged out-of-hospital cardiopulmonary resuscitation. Am J Cardiol 73:953–955

A retrospective study by Van Campen et al. [9] on patients with AMI who required CPR evaluated the safety and efficacy of thrombolytic therapy, comparing outcomes between 33 patients treated with thrombolysis and 39 without it. They excluded patients who first received thrombolysis and then needed CPR. The two groups were similar in gender, infarction type, comorbidities, age, etc. There were 13 non-survivors (30.4%) among the patients receiving thrombolysis versus 24 (66.7%) among those not receiving it. The mean duration of the CPR was 20.7 ± 19.2 min in the group treated with thrombolysis and 23.5 ± 14.6 min in the group treated without thrombolysis. The neurological injuries and complications were similar and there was only one fatal gastric hemorrhage with thrombolysis that was not attributable to the CPR. The authors concluded that the administration of thrombolysis after CPR is safe (it does not increase hemorrhagic complications) and efficacious (it contributes to a reduction in mortality).

Other groups have also reported the administration of thrombolysis to be safe [10, 11, 12, 13, 14]. Cross et al. [10] described 39 patients with AMI that suffered cardiac arrest, of whom ten presented cardiac arrest before thrombolysis, with five of these ten requiring external heart massage and the other five only defibrillation. No patient suffered a fatal complication and just one patient presented a mild retrosternal hematoma; the authors concluded that CPR is not a clear contraindication for thrombolysis. Tenaglia et al. [11], in 1991, retrospectively studied the complications of thrombolysis in 708 patients with AMI who had received CPR. Among the 59 patients (8%) that required CPR of less than 10 min, there were no differences in complications, number of transfusions or length of stay between patients treated with thrombolysis and those who were not. They concluded that thrombolysis with a CPR of short duration is safe and causes no additional complication attributable to the thrombolytic therapy, and that these patients may benefit from the treatment. It should be noted that it cannot be inferred that thrombolysis after a longer CPR is unsafe, and the authors themselves recognized the selection bias of their study caused by their exclusion of patients receiving CPR of over 10 min.

Scholz et al. [12] retrospectively analyzed the influence of CPR on thrombolysis among 2147 patients with AMI, of whom 590 patients received thrombolysis, with 43 of these undergoing prolonged CPR within 24 h of the thrombolysis. The mean duration of the

CPR was 36 ± 32 min (range, 4–120 min). Patients who had only defibrillation without cardiocompression were not included in the CPR group. Among the patients receiving thrombolysis, there were no significant differences between the CPR and non-CPR groups. The thrombolysis was administered during cardiocompression in six cases and the resuscitation was effective in two of these. Hemorrhagic complications developed in 8 of the 43 resuscitated patients that received thrombolysis: injection site bleeding in three patients, gastrointestinal bleeding in two, mild genitourinary bleeding in one and bleeding without site identification in the remaining two. There was no significant difference in the rate of bleeding complications between the 43 patients with mechanical resuscitation and the 547 patients without it (18.6 versus 16.1 %).

Fischer M, Böttiger BW, Popov-Cenic S, Hossmann KA (1996) Thrombolysis using plasminogen activator and heparin reduces cerebral no-reflow after resuscitation from cardiac arrest: an experimental study in the cat. *Intensive Care Med* 22:1214–1223

One issue widely studied experimentally in the context of cardiac arrest is cerebral protection. The brain damage produced during cardiac arrest depends on the duration of the ischemia and on secondary injuries caused by post-ischemic hypoperfusion or cerebral no-reflow phenomenon. The severity of this phenomenon is modulated by the duration of the ischemia, the reperfusion pressure and activation of the coagulation cascade, which generates microthrombi in the pial vessels of the cerebral cortex. Fischer et al. [15] studied the effect of alteplase on the cerebral no-reflow phenomenon in 14 cats. They reported a significant reduction in the cerebral no-reflow phenomenon with no hemorrhagic complications and concluded that thrombolytic therapy could optimize cerebral resuscitation by improving the microcirculatory reperfusion of the cat brain when administered during reperfusion after cardiac arrest.

Discussion

The studies considered in the present paper suggest that thrombolysis offers a possible benefit to patients with AMI, and perhaps with FPE, who require CPR. Undoubtedly this approach is not risk-free, although it is not the only risky measure applied to patients in cardiac arrest, when many CPR maneuvers are performed with no sound scientific foundation [16] and involve the possibility of some type of complication. Thus, many authors are beginning to recommend this therapeutic approach in cases of AMI and FPE that need CPR [7, 8, 9, 10, 11, 12, 17]. They consider that the administration

of a fast-acting thrombolytic of short half-life and proven efficacy, such as alteplase or reteplase, may be tremendously useful as well as permitting subsequent surgery when necessary.

One of the reasons for the failure of CPR in these patients is that it does not solve the problems that cause it to be attempted. Thrombolysis can act on the etiology of the cardiac arrest through several mechanisms and can achieve a minimum, but sufficient, hemodynamic improvement and stabilization to enable the patient to be resuscitated. The following stand out among these possible mechanisms of action: (1) Immediate coronary reperfusion, (2) Release of the pulmonary artery through total or partial lysis of the embolism in FPE, (3) Reduction in the viscosity of the blood through the fibrinogenolysis phenomenon, with a resulting improvement in the pulmonary or systemic circulation and (4) Improvement of cerebral perfusion through limitation of cerebral no-reflow.

One of the problems is to know when thrombolytic therapy is indicated. Thrombolysis seems to be very safe with CPR of less than 10 min, while it has not been demonstrated that its administration in cases of longer CPR increases the risk of complications. It seems reasonable to make the decision after an assessment of its potential risks and benefits in each case [18] and to decide against thrombolysis when the CPR is very traumatic and there is evidence or strong suspicion of injuries [19] or when thrombolysis is clearly contraindicated and other types of revascularization could be used, such as angioplasty or bypass in AMI or embolectomy in cases of FPE.

Another issue is the selection of patients to receive thrombolysis during CPR. How do we know whether the origin of the cardiac arrest is an AMI or an FPE? In reality, we cannot be sure [8, 20], and the diagnosis must be based on suggestive and compatible clinical symptoms and history or on such techniques as echocardiography during the CPR, although a certain degree of diagnostic error must be expected. In cases where the cause of the cardiac arrest is stroke, there is no indication, in principle, although research is currently under way on the effectiveness and safety of thrombolysis during the acute phase of stroke without cardiac arrest [21]. As well as the theoretic benefit of thrombolysis during CPR, experimental studies suggest that it may limit cerebral no-reflow, with a consequent improvement in cerebral perfusion and in neurological results during the resuscitation [15]. Thus, it cannot a priori be ruled out that this therapy may one day become just one more of the normal measures in CPR.

In conclusion, thrombolytic therapy can be considered a sound approach and not contraindicated during or after an AMI that requires CPR maneuvers, except when the CPR is aggressive or in the presence of an ac-

tive hemorrhage or for patients with multiple trauma. The few studies on patients with FPE who require CPR suggest that it may also be very effective in this setting. Nevertheless, we must be aware that there has been no study of a sufficiently high scientific evidence level to

elucidate the role of thrombolysis in cardiac arrest. The great therapeutic potential of this approach makes urgent a clinical trial for a reliable assessment of its safety and efficacy.

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