Massive fibrinolysis after cardiopulmonary resuscitation in a 39-year-old woman

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Abstract
This case report describes massive fibrinolysis after prolonged cardiopulmonary resuscitation. Lab results revealed unexpected clotting abnormalities, with infinitely prolonged clotting times and an immeasurably low fibrinogen concentration. Severe haemorrhage occurred with haemodynamic instability and failure of mechanical ventilation. Post mortem, the observed clotting abnormalities where interpreted as hyperfibrinolysis, caused by hypoperfusion. This mechanism, and other causes of abnormal haemostasis post-resuscitation, are discussed in this paper. Hyperfibrinolysis is associated with severe hypoperfusion leading to endothelial damage and glycocalyx breakdown and correlated with lactate levels and chest compression times. Significant fibrinolysis after cardiopulmonary resuscitation occurs more frequently than clinicians may think, and thromboelastography might be useful to detect and possibly treat hyperfibrinolysis early. In this case, severe haemorrhage was the immediate cause of death after successful return of spontaneous circulation.

Introduction
The circulatory stress associated with cardiac arrest and the consequent cascade of cytokine activation can have profound effects on haemostasis. Conventional wisdom prepares the clinician for activation of the clotting system. We report on a case that showed the opposite: severely impeded coagulation after cardiopulmonary resuscitation (CPR). Further analysis suggested massive fibrinolysis as the offending mechanism.

Case report
A 39-year-old female patient was brought to the emergency department after an out-of-hospital cardiac arrest. During childhood she had undergone operative repair of an atrial septum defect, resulting in mild mitral valve insufficiency which had not been controlled for several years. On the morning of the event she had visited her general practitioner with complaints of general discomfort and dry cough. High blood pressure was measured (200/100 mmHg), but because secondary signs were absent (no pulmonary crepitations on auscultation, no oedema, no headache or problems with sight were noted) she was not put on any antihypertensive medication. Instead, the patient was referred to her cardiologist to consult about her hypertension. Immediately before the cardiac arrest, she had caused a traffic accident on a parking lot and had rung her husband in an anxious state, reporting that she was unwell and asking her husband to call the emergency services. Shortly after this telephone conversation, she collapsed. Whether her circulatory state prior to the arrest was the reason for the accident remains uncertain.

On arrival of the ambulance, basic life support had been started; the initial rhythm was asystole. She was intubated and advanced life support was continued at the scene for 35 minutes, during which a total of 5 mg of epinephrine was given. She was brought to the emergency department whilst manual chest compressions were being continued. Rhythm checks during transport revealed bradycardia without a palpable pulse. Approximately 70 minutes after the initial collapse the patient regained sinus rhythm with output and was transferred to the intensive care unit (ICU). Immediately after the return of spontaneous circulation, echocardiography showed ventricular contractions with globally diminished ventricular wall motions and an intermediate to severe mitral valve insufficiency. The right ventricle was not dilated. ECG showed a left bundle branch block. Our working diagnosis was: hypoxic cardiac arrest caused by acute left heart failure with pulmonary oedema in a patient with pre-existent mitral valve insufficiency, new-onset hypertension and a stressful event. In the ICU, the circulation was supported with high doses of norepinephrine and several doses of epinephrine. She was ventilated with an oxygen concentration of 100% and increasingly high airway pressures. A catheter was placed in
the pulmonary artery, showing low filling pressures, and a low stroke volume. Even after fluid resuscitation with crystalloids, the blood pressure remained low. Hypoperfusion was evident, with a serum lactate of 19.6 mmol/l; aspartate transaminase and alanine aminotransferase were both >1700 U/l, indicating acute hepatocyte damage. An echocardiogram showed a well-contracting, but nearly empty left ventricle. These findings argued against acute heart failure, and pointed towards intravascular volume depletion, so volume resuscitation was continued. Laboratory results revealed unsuspected clotting abnormalities with infinitely prolonged clotting times and an unmeasurably low fibrinogen concentration. Immediately, 2 g of fibrinogen was administered, along with sodium bicarbonate to correct the metabolic acidosis. Haematomas in the groin developed where intravenous and intra-arterial catheters had been inserted, for which pressure bandages were applied. After 1000 ml of blood had been evacuated from the nasogastric tube, continuous infusion with a proton pump inhibitor was started. An abdominal ultrasound revealed no blood in the abdominal cavity. Haemodynamic instability continued, with frequent loss of cardiac output, and advanced life support was repeated several times. Ultrasound examination continued to indicate hypovolaemia, and laboratory results revealed a continuing clotting disorder (activated partial prothrombin time >240 sec, prothrombin time >120 sec), which was not understood at the time. A working hypothesis of diffuse intravascular coagulation with depletion coagulopathy was adopted.

In the following two hours, eight units of erythrocyte concentrate and four units of fresh frozen plasma were administered, along with another 4 g of fibrinogen and 1000 mg of tranexamic acid. In total, 9.5 litres of fluids were administered. Ventilatory pressures kept rising, eventually hypercapnia developed and no adequate oxygenation could be achieved. Five hours after ICU admission, treatment was discontinued. The patient died soon after mechanical ventilation was discontinued.

**Post mortem**

Autopsy revealed no pulmonary embolus or primary haemorrhage. Cerebral tissue revealed no abnormalities, notably no subarachnoid bleeding. Lungs and liver showed signs of acute left heart failure. No signs of diffuse intravascular coagulation were seen. It was concluded that death was caused by a primary cardiac event, complicated by clotting abnormalities and haemorrhage. Post mortem, blood samples taken in the emergency department were re-examined, revealing an immeasurably low fibrinogen and high D-dimer (>20,000 µg/l). Thromboelastography was not available at our centre. It was not until then that we understood that massive fibrinolysis and consumption of fibrinogen was the most likely cause of the clotting abnormalities and haemorrhage in this patient.

**Discussion**

This patient developed severe coagulopathy early in the post-resuscitation phase after CPR that lasted approximately 70 minutes. As a general rule, in our hospital, resuscitation attempts are terminated when spontaneous circulation has not returned after 20 minutes in case of asystole with no reversible cause, but exceptions do apply. In this case, it concerned a young woman, with a well-defined interval between collapse and arrival of the emergency services, in whom seemingly adequate bystander CPR had been applied. Had we used the Go-FAR score in this patient, a scale developed for predicting outcome after attempted resuscitation, she would have received the highest score. On arrival to the hospital, resuscitation had already been going on for 45 minutes, and at that time the attending intensivist and cardiologist decided that prolonging the CPR was justified, with the intention to give this resuscitation one last chance with all hospital services in place. In retrospect, the high lactate concentration, combined with sky-high liver enzymes and the massive coagulation disorder that followed, all indicated severe hypoxic damage to multiple organs. Favourable neurological outcome would have been extremely unlikely. However, after another 20 minutes of in-hospital CPR, spontaneous circulation returned and the patient entered a stable haemodynamic interval. Obviously, the team was not well prepared to deal with the massive coagulopathy that ensued after spontaneous circulation had returned. The patient started bleeding soon after admission to the ICU, and all attempts to correct the coagulopathy remained futile. After massive transfusion and aggressive attempts to correct the bleeding disorder, she died of haemorrhagic shock.

What may have prohibited adequate treatment was that the exact nature of the clotting abnormality was not immediately clear. Was this bleeding disorder something that the attending team should have anticipated? During cardiac arrest a state of tissue hypoperfusion and ischaemia exists. In the 1970s, Negovsky described a complex phase of resuscitation starting after spontaneous circulation had returned, which later became known as the post-resuscitation syndrome. This syndrome is characterised by several pathophysiological processes including brain injury, myocardial dysfunction and a systemic ischaemia/reperfusion response. Recently, the European Society of Cardiology (ESC) published updated guidelines, containing a chapter on the post-resuscitation syndrome. Post-resuscitation care should focus on preventing and attenuating various forms of organ failure that can be expected after CPR. In this guideline, an overall activating effect on the clotting system in the first phase after cardiac arrest is incidentally mentioned. At present, we are not aware of guidelines that recommend urgent coagulation testing after CPR, neither routine tests, nor thromboelastometry. We think that the principal learning point from this case is that, if looked for, clotting abnormalities after CPR are quite...
common. A number of mechanisms have been put forward. Adrie et al. surveyed 67 consecutive patients after successful CPR and found that a majority of them had abnormal coagulation biomarkers, with more profound abnormalities in non-survivors. The coagulopathy followed a pattern similar to the systemic inflammatory response seen in septic shock, with hypercoagulability and disseminated intravascular coagulation, resulting in consumptive coagulopathy. The initial hypercoagulability was attributed to down-regulation of protein C and S levels, secondary to endothelial damage.[6] In this model, activated coagulation was an early step in the development of organ failure. The microthrombi formed in this process, combined with intravascular fibrin deposition and insufficient fibrin removal, acted as offending mechanisms, contributing to impaired reperfusion and possible multi-organ failure after cardiac arrest.[5,7,8]

Another theory to explain coagulopathy after cardiac arrest is glycocalyx injury. A number of recent studies looking at biomarkers of glycocalyx degradation showed that the increase in circulating catecholamines after myocardial infarction or cardiac arrest correlated not only with markers of endothelial cell damage, but also with an increased release of glycocalyx components. One of those components was heparan sulphate, which is a heparin-like agent, thus contributing to a hypocoagulable state.[9,10]

Whatever the chain of events might be, following activation of coagulation one would expect enhanced fibrinolysis to occur as a counterbalance. Remarkably, this was not observed in early work done by Bottiger et al. who described an activated clotting cascade, without accompanying hyperfibrinolysis.[11] However, later studies were able to convincingly demonstrate enhanced fibrinolysis after cardiac arrest.[6,7,9,12]

A possible mechanism for this hyperfibrinolytic state after cardiac arrest is that hypoperfusion increases epinephrine and vasopressin levels, leading to a release of tissue plasminogen activator (t-PA) from endothelial cells, which in turn causes high levels of plasmin. Excess plasmin may then lead to hyperfibrinolysis. This theory was supported by Dudevket et al., showing that activation of the fibrinolytic system was more common in patients after out-of-hospital cardiac arrest with an initial oxygen saturation of 50% or less and is linked to increased levels of t-PA.[12] The release of t-PA may actually benefit from the earlier described release of protein C, which limits the action of plasminogen activator inhibitor 1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI). All these processes work together to enhance fibrinolysis.[7,8]

Some degree of hyperfibrinolysis, which can be detected by thromboelastography at the point of care, occurs in almost half of post-resuscitation patients. Two studies have focussed on hyperfibrinolysis after cardiac arrest. One study revealed that 35.8% of patients showed hyperfibrinolysis,[7] another study showed this phenomenon in 53% of patients.[8] A correlation seemed to exist between chest compression time and lactate with the onset of hyperfibrinolysis, suggesting an association between the degree of hypoperfusion and hyperfibrinolysis.[10] In our patient, this relation between the duration of CPR, hypoperfusion indicated by a high lactate and extreme fibrinolysis was clearly illustrated.

Two clinical studies identified hyperfibrinolysis as a poor prognostic sign.[7,8] In the case of our patient, one might think that a point of no return had already been reached before she arrived at the emergency department. This raises the question what could have been done in order to improve the outcome in this situation. Initial resuscitation was performed with intravenous fluids and packed red blood cells. Fresh frozen plasma and tranexamic acid were administered at a later stage, both aimed to treat coagulopathy in the face of profuse bleeding.

Was administering procoagulants the right thing to do? In a recent animal study, using a model of ischaemia and reperfusion, tranexamic acid given early on was shown to reverse hyperfibrinolysis.[13] The administration of tranexamic acid might in theory be beneficial, but to our knowledge, therapeutic or preventive use after cardiac arrest in humans has not been described. However, there is some clinical evidence that antifibrinolytic drugs can be beneficial in trauma resuscitation, in which the phenomena of coagulopathy and hyperfibrinolysis are well defined and show similarities to the post-cardiac arrest situation. Several trials in bleeding trauma patients have shown that antifibrinolytic agents reduced the risk of death due to haemorrhage when given early in the course.[14,15] However, administrating tranexamic acid more than three hours after the injury led to an increased risk of death due to bleeding in trauma patients. It has been hypothesised that patients in the late phase of trauma would develop disseminated intravascular coagulation, a situation in which tranexamic acid could be contraindicated.[14] Assuming that reducing coagulability is an evolutionary mechanism to maintain flow in an injured and procoagulant microcirculation, one could argue that administering procoagulants is counterproductive. With these considerations in mind, and given the lack of clinical data on the use of antifibrinolytic drugs in the treatment of post-resuscitation coagulation abnormalities, the routine use of these agents cannot be recommended. However, in a situation where the clinician is with his back against the wall, compassionate use may be justified. In our patient, the degree of hyperfibrinolysis and acidosis was so severe that we are inclined to think that the process of hyperfibrinolysis would not have been reversible, even if antifibrinolytics had been given earlier in the course.

**Conclusion**

In prolonged CPR after cardiac arrest, massive coagulopathy and fibrinolysis can occur, which can be detected by thromboelastography. Hyperfibrinolysis is associated with hypoperfusion and correlated with lactate levels and chest
compression times. The use of thromboelastography in patients with cardiac arrest could be useful to detect fibrinolysis early.

Disclosures
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