

Postresuscitation disease after cardiac arrest: a sepsis-like syndrome?

Christophe Adrie,^a Ivan Laurent,^b Mehran Monchi,^b Alain Cariou,^c Jean-François Dhainau^c and Christian Spaulding^d

Purpose of review

Despite advances in cardiac arrest resuscitation, neurologic impairments and other organ dysfunctions cause considerable mortality and morbidity after restoration of spontaneous cardiac activity. The mechanisms underlying this postresuscitation disease probably involve a whole-body ischemia and reperfusion syndrome that triggers a systemic inflammatory response.

Recent findings

Postresuscitation disease is characterized by high levels of circulating cytokines and adhesion molecules, the presence of plasma endotoxin, and dysregulated leukocyte production of cytokines: a profile similar to that seen in severe sepsis. Transient myocardial dysfunction can occur after resuscitation, mainly as a result of myocardial stunning. However, early successful angioplasty is independently associated with better outcomes after cardiac arrest associated with myocardial infarction. Coagulation abnormalities occur consistently after successful resuscitation, and their severity is associated with mortality. For example, plasma protein C and S activities after successful resuscitation are lower in nonsurvivors than in survivors. Low baseline cortisol levels may be associated with an increased risk of fatal early refractory shock after cardiac arrest, suggesting adrenal dysfunction in these patients.

Summary

Postresuscitation abnormalities after cardiac arrest mimic the immunologic and coagulation disorders observed in severe sepsis. This suggests that therapeutic approaches used recently with success in severe sepsis should be investigated in patients successfully resuscitated after cardiac arrest.

Keywords

heart arrest, severe sepsis, cardiopulmonary resuscitation, reperfusion, coagulation.

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^aIntensive Care Unit, Delafontaine Hospital, Saint Denis, France, ^bIntensive Care Unit, Jacques Cartier Institute, Massy, France, ^cIntensive Care Unit, Cochin Hospital, René Descartes University, Paris, France and ^dCardiology Department, Cochin Hospital, René Descartes University, Paris, France

Correspondence to Christian Spaulding, Cardiology Department, Cochin Hospital, 27 rue du Faubourg Saint Jacques, Paris Cedex 75679, France
Tel: 33 (0)1 58 41 16 57; Fax: 33(0)1 58 41 16 05;
e-mail: christian.spaulding@cch.ap-hop-paris.fr

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Introduction

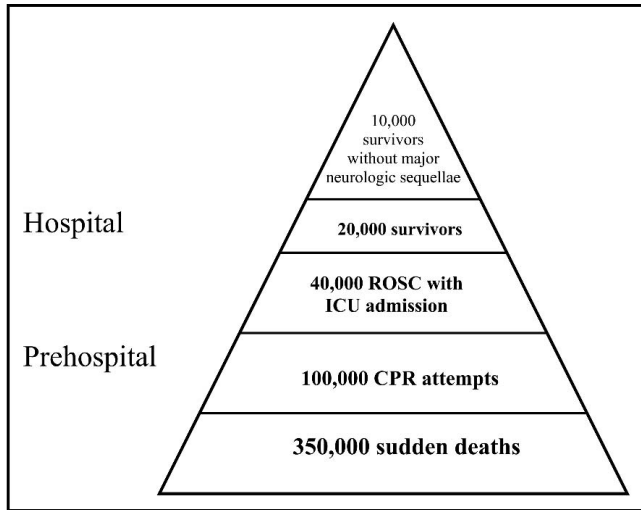
At least 225,000 out-of-hospital deaths resulting from coronary heart disease occur each year in the United States. In addition, an estimated 370,000 to 750,000 patients undergo resuscitation for in-hospital cardiac arrest each year. Ischemic cardiovascular disease is by far the most common cause of cardiac arrest in adults. No national statistics on survival after out-of hospital cardiac arrest are available for the United States. Community-wide studies found rates ranging from 4% to 33% depending on the chain of survival (Fig. 1) [1,2]. Since the introduction of modern cardiopulmonary resuscitation and emergency cardiovascular care 50 years ago, considerable progress has been achieved in the management of cardiac arrest. Nevertheless, patients admitted to the intensive care unit after successful resuscitation have a poor prognosis and a high risk of postresuscitation disease, a condition of multiple life-threatening disorders, including neurologic failure [3]. Recent reports of higher survival rates in patients treated with mild hypothermia after successful resuscitation from cardiac arrest confirm that the outcome is determined not only by the time to circulation recovery but also by pathogenic processes that are triggered by the cardiac arrest, then continue to evolve subsequently, causing damage to the nervous system and other organs [4,5]. Improved understanding of these pathogenic processes can be expected to open up new avenues for research and treatment aimed at preventing both (1) death resulting from early refractory shock with multiple organ dysfunction and (2) secondary development of brain damage.

Postresuscitation disease is a constellation of disorders related to whole-body ischemia and reperfusion syndrome. It shares many features with severe sepsis, including plasma cytokine elevation with dysregulated cytokine production, the presence of endotoxin in plasma, coagulation abnormalities, and adrenal dysfunction.

Systemic inflammatory response syndrome

Components of the systemic inflammatory response syndrome are the ischemia and reperfusion syndrome, the inflammatory response, myocardial dysfunction, coagulopathy, and adrenal dysfunction.

Figure 1. Survival rates after cardiac arrest remain low in patients who recover spontaneous circulation



Recent studies identified a patient subset with higher survival rates and confirmed that the outcome was dependent in part on pathophysiologic disturbances observed after successful resuscitation. ROSC, return of spontaneous circulation. Adapted from [2].

Ischemia and reperfusion syndrome

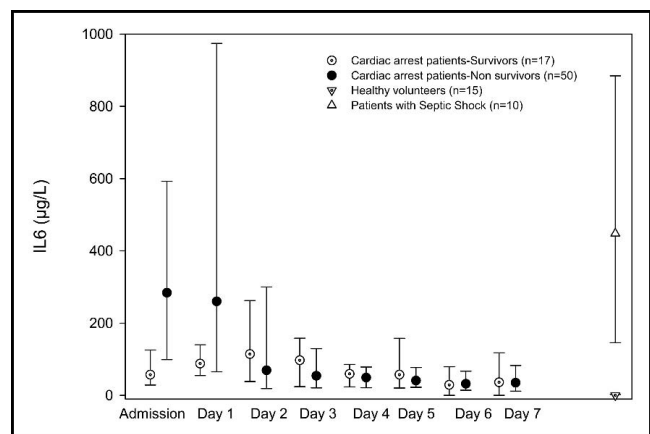
Although prolonged ischemia results in severe tissue and organ damage, reperfusion-induced injury—defined as tissue damage directly related to revascularization—may be even more harmful [6]. This is a major concern in cardiac arrest patients, because successful resuscitation leads to whole-body ischemia and reperfusion injury. During the ischemic phase, hypoxia *per se* is thought to be a key cause of tissue damage. Oxygen deprivation precludes oxidative phosphorylation in the mitochondria, leaving the anaerobic pathway as the only available source of ATP. Consequently, cellular ATP levels drop. During the reperfusion phase, blood reflow may lead to further damage, a phenomenon known as the oxygen paradox and apparently related to the perpetuation of events initiated during the ischemic period. Whereas the severity of reperfusion injury varies with the duration of ischemia, other factors influence the extent of tissue damage, including O₂ concentration, temperature, and pH. The release of oxygen free radicals, coagulation and complement-activation products, and cytokines during reperfusion leads to marked activation of neutrophils with up-regulation of their surface adhesion molecules. The activated neutrophils bind to endothelial ligands, then exit the vascular compartment, migrating to the area of tissue injury [7]. Leukocyte adhesion is a critical step in vascular endothelium injury, leading to increased microvascular permeability and thrombosis. Importantly, mucosal gut lesions after ischemia and reperfusion injury cause widespread functional impairment with increased permeability of the mucosal barrier, diarrhea, and endotoxin or bacterial translocation. Endotoxins and bacteria

in the bloodstream may contribute to the genesis of tissue damage and therefore to multiple organ dysfunction.

Inflammatory response

Sharp rises in various cytokines and soluble receptors occur in the bloodstream as early as 3 hours after cardiac arrest. Several cytokines show greater elevations in non-survivors than in survivors (Fig. 2) as well as in patients requiring vasopressor therapy, compared with other patients. The levels of cytokines such as interleukin-6 and soluble tumor necrosis factor receptor II are closely correlated with lactate, a marker for tissue hypoxia, suggesting a close relation between ischemia and reperfusion syndrome and inflammatory responses [8••]. Translocation of endotoxins through sites of gut-wall ischemia and reperfusion damage may explain the increased plasma endotoxin levels noted within 2 days after successful resuscitation. However, no correlation was found between plasma endotoxin levels and mortality [8••]. Soluble intercellular adhesion molecule-1, soluble vascular-cell adhesion molecule-1, and P and E selectins were increased during and after cardiopulmonary resuscitation, suggesting neutrophil activation and subsequent endothelial injury [9–11]. Interestingly, hyporesponsiveness of circulating leukocytes, as assessed *ex vivo*, has been extensively studied in patients with systemic inflammatory response syndrome related to sepsis, trauma, or recovery from cardiac arrest [8••,12–14]. This phenomenon, known as endotoxin tolerance, seems to affect monocytes and neutrophils as well as lymphocytes and to be dependent on the activating signal. It may allow protection against overwhelming dysregulation of the pro-inflammatory process, but, by contrast, it may induce immune paralysis (or endogenous immunosuppression)

Figure 2. Plasma interleukin-6 (IL-6) kinetics over 7 days in patients who were successfully resuscitated after cardiac arrest



Seventeen patients survived without neurologic dysfunction. Levels of interleukin-6 (IL-6) were sharply increased, and the levels were significantly higher in those who did not survive. Patients with severe sepsis constituted a positive control group, and healthy volunteers constituted a negative control group. Data are expressed as median ± interquartile range.

with an increased risk of subsequent nosocomial infection [15]. In patients with out-of-hospital cardiac arrest, abnormalities in leukocyte regulation vary with the cytokines studied and the nature of the stimulating agent. Plasma from resuscitated patients can diminish LPS-induced activation of leukocytes from healthy donors *in vitro*, establishing that whole-blood hyporesponsiveness to endotoxin is caused by soluble serum factors released systemically after cardiac arrest. Furthermore, intrinsic leukocyte functions seem to be affected, because *ex vivo* substitution of healthy donor plasma for patient plasma fails to restore a normal response to endotoxin [8••,13,14]. The cause of this inflammatory response syndrome is probably ischemia and reperfusion syndrome responsible for endotoxemia, as well as bacteremia as described in dogs and humans [16,17]. In addition, gastric aspiration is very common in cardiac arrest patients and, even when minimal, may contribute to induce an inflammatory response.

Myocardial dysfunction

Animal studies support the concept that postresuscitation hemodynamic instability is related to acute myocardial dysfunction characterized by impaired contractile function, decreased work capacity, and variable diastolic dysfunction, which resolve within hours or days after the return to spontaneous circulation [18–21]. Acute myocardial dysfunction was prevented by early dobutamine infusion in a swine model and was shown to indicate global myocardial stunning [18]. Transient hemodynamic instability and myocardial dysfunction have also been investigated in humans [22,23•,24]. For instance, in three patients younger than 40 years of age who survived cardiac arrest due to ventricular fibrillation, idiopathic dilated cardiomyopathy was diagnosed immediately after the cardiac arrest. However, follow-up investigations showed normal or near-normal function 2 weeks later [24]. These findings suggest that myocardial stunning due to hypoperfusion during ventricular fibrillation or the effects of transthoracic electrical shocks may result in profound but reversible myocardial depression. The potential mechanisms involved have been investigated recently in a large cohort of patients resuscitated after cardiac arrest presumably caused by cardiac disease [23••]. Postresuscitation myocardial dysfunction was a consistent finding, even in patients without hemodynamic instability or coronary heart disease. The onset of hemodynamic instability was often delayed, occurring 4 to 7 hours after admission, and full recovery was seen in survivors within 72 hours. Postresuscitation hemodynamic instability was more common in patients with acute coronary occlusion as the cause of cardiac arrest, high-dose epinephrine therapy, or longer duration of cardiopulmonary resuscitation. Interestingly, mortality from early refractory shock (13.5%) after successful angioplasty compared favorably with mortality (19.1%) from refractory shock in patients without acute myocardial infarction [23••]. Fur-

thermore, successful angioplasty improved survival in patients resuscitated after cardiac arrest [25]. This may be related to myocardial salvage with a lower rate of arrhythmia recurrence and better reversal of myocardial dysfunction.

Interestingly, although cardiac output increased rapidly in patients receiving vasoactive drugs, a large amount of volume expanders was required initially (cumulative crystalloid volume, 5000 [3500–6500] ml at 24 hours) to maintain filling pressures just above 12 mm Hg (a rather low value, considering the myocardial dysfunction), resulting in hemodilution [23••]. Together with the sharp increases in cytokines and presence of endotoxin in plasma [8], the need for large amounts of fluids suggests that vasoplegia may occur after cardiac arrest, as in severe sepsis, and may play a key role in hemodynamic instability [8••,23••]. Conceivably, the acute myocardial dysfunction may be induced in part by circulating depressant factors, including the cytokines tumor necrosis factor- α and interleukin-1 β , as observed in sepsis [26].

Coagulopathy

Marked alterations in coagulation have been reported after cardiac arrest in both experimental and human settings [8••,16,27,28]. Coagulation/anticoagulation and fibrinolysis/antifibrinolysis systems are activated in patients undergoing cardiopulmonary resuscitation, particularly those who recover spontaneous circulation. Thrombin-antithrombin complex as a marker of coagulation activation was consistently elevated, whereas anticoagulant factors such as antithrombin, protein S, and protein C were decreased [27]. Fibrinolysis activation, as assessed by the plasmin-antiplasmin complex, was also universally observed, and some patients had inhibition of fibrinolysis, with PAI-1 elevation at admission followed by a further increase on the next day [27]. No marked increases were found in plasma levels of D-dimer, another indicator of endogenous fibrinolytic activity, suggesting that blood coagulation and fibrin formation were not adequately counteracted by endogenous fibrinolysis [28]. However marked D-dimer elevation was found in another study in which all patients had lasting restoration of spontaneous circulation [27].

Only a very transient increase in endogenous activated protein C was observed in out-of-hospital cardiac arrest patients at admission very shortly after the cardiac arrest-resuscitation event (Adrie *et al.*, unpublished data). The generation of activated protein C in plasma in healthy humans is dependent on the circulating concentrations of both protein C and thrombin. However, in patients with severe sepsis, the conversion of endogenous protein C to activated protein C may be impaired because of endothelial dysfunction with down-regulation of thrombomodulin and endothelial protein-C receptor [29]. In contrast to severe sepsis in humans, cardiac arrest repre-

sents an acute event occurring at a well-defined time, so that early changes in systemic biomarkers can be detected. Early endothelial stimulation and thrombin generation may be responsible for the tremendous increase in protein C activation, followed rapidly by a phase of endothelial dysfunction in which the endothelium may be unable to generate an adequate amount of activated protein C. The rise in activated protein C may reflect a natural compensatory mechanism that dampens the coagulation activation and inflammatory response triggered by cardiac arrest and resuscitation. Disseminated intravascular coagulation is characterized by thrombin generation and fibrin deposition, resulting in widespread microvascular thrombosis, which in turn causes multiple organ failures, including neurologic impairments. Coagulation disorders after successful resuscitation for cardiac arrest may cause both ischemic lesions and reperfusion damage of the brain. Of interest, activated protein C has been shown to minimize ischemia and reperfusion injury in experimental models of spinal cord damage and stroke [30–32].

Adrenal dysfunction

As observed in severe sepsis, the integrity of the hypothalamic-pituitary-adrenal axis can be impaired by many mechanisms, leading to adrenal insufficiency with extensive destruction of adrenal tissue, most notably in patients with underlying coagulopathy. High levels of inflammatory cytokines can directly inhibit the production of cortisol by the adrenals. For instance, in humans, exogenous interleukin-6 causes a dramatic and prolonged elevation in plasma ACTH and cortisol on the first day, followed by a blunted response to corticotropin. Both inflammation and coagulopathy have been described after successful circulatory arrest resuscitation [8••,27]. Annane *et al.* [33] and Annane [34] showed that the adrenal response to exogenous corticotropin was helpful in identifying patients with septic shock at high risk of death, and replacement therapy with low-dose corticosteroids decreased mortality rates in patients with adrenal insufficiency, defined as failure to increase plasma cortisol to 9 µg/dL or more in response to injected corticotropin.

Schultz *et al.* [35] found that serum cortisol levels during and after cardiac arrest were elevated, but not as much as after such a severe stress. Corticotropin induced no significant response when the mean group value was considered, but the study did not attempt to distinguish responders from nonresponders. Recently, fairly high baseline cortisol levels were found, contrasting with a 42% prevalence of relative adrenal insufficiency, defined as failure to respond to corticotropin (Hékimian *et al.*, unpublished data). A similar prevalence of relative adrenal insufficiency was noted in septic shock patients admitted during the study period. In this pilot study, the response to corticotropin was not associated with the

usual disease severity markers or with the cause of death (early refractory shock or neurologic dysfunction). However, baseline cortisol levels measured within 6 to 36 hours after the onset of cardiac arrest were lower in patients who subsequently died of early refractory shock than in patients who died later of neurologic failure, suggesting adrenal insufficiency in the former group (Hékimian *et al.*, unpublished data).

The difference between baseline cortisol levels in patients who died of early refractory shock and in those who died of neurologic dysfunction may have important implications. Laurent *et al.* [23••] showed that hemodynamic instability, a common problem between 6 and 24 hours after resuscitation, was not predictive of the neurologic outcome. This suggests that cortisol replacement therapy may help some patients to recover from early refractory shock and perhaps also achieve a good neurologic recovery. However, a larger study is required to obtain additional information on adrenal function after cardiac arrest and on the possible benefits of low-dose corticosteroid replacement therapy.

Therapeutic prospects

Various aspects of the hemostasis alterations seen after recovery of spontaneous circulation mimic those observed in severe sepsis. As stated before, the protective role of hypothermia in highly selected patients with a fairly good prognosis (control groups had survival rates close to 35%) suggests that the postresuscitation processes described above may contribute to the induction of secondary neurologic deterioration and that specific treatments may improve survival rates. High-volume hemofiltration has been shown to be of value in children after extracorporeal circulation for cardiac surgery, another model of whole-body ischemia and reperfusion. We [36] evaluated the potential benefits of high-volume hemofiltration (100 L of fully balanced ultrafiltration over an 8-hour period) by randomizing 61 patients with out-of-hospital cardiac arrest into three groups: control patients and those with high-volume hemofiltration with or without hypothermia. High-volume hemofiltration improved survival, and adding hypothermia might have provide further survival gains. However, this difference was not significant: more than 200 patients in each group would be needed to produce sufficient power for detecting a statistically significant difference between high-volume hemofiltration with and without hypothermia [36]. In addition to a potential role in controlling inflammatory processes, this extracorporeal technique readily reduces body temperature to the desired range (32–33°C) within 1 hour in most cases.

Conclusion

The postresuscitation phase after out-of-hospital cardiac arrest is characterized by a systemic inflammatory response similar to that observed in other systemic inflam-

matory conditions such as severe sepsis. This should prompt large-scale randomized trials of the treatments currently used in severe sepsis, such as low-dose replacement corticosteroid therapy and/or rhAPC, in patients successfully resuscitated after cardiac arrest.

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