The Potential Contribution of Corticosteroids to Positive Cardiac Arrest Outcomes

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14.1 Introduction

Over the past 50 years, the majority of research on cardiac arrest has focused on improving the rate of return of spontaneous circulation (ROSC); however, many interventions improved ROSC without improving long-term survival. The translation of optimized basic life support and advanced life support interventions into the best possible outcomes is sine qua non in optimal post-arrest care. There is a scarcity of data reported from the post-arrest in-hospital phase, and no generally accepted, evidence-based protocol exists, other than brain protection-oriented intensive care. For any further improvement in post-arrest care, we first have to determine the relative contribution of potential, outcome-determining factors [1].

The importance of these factors leads to the addition of a fifth ring, post-resuscitation care (Fig. 14.1), to the ''Chain of Survival.'' The idea is not new; the hospital ring was included by Niemann [2] in 1982, and more recently, by Engdahl et al. [3].

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A. Gullo and G. Ristagno (eds.), *Resuscitation*,
DOI: 10.1007/978-88-470-5507-0_14,

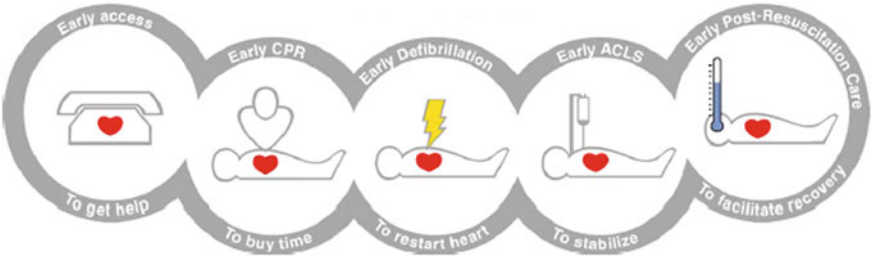


Fig. 14.1 The chain of Survival. Reproduced with permission from Ref. [1]. *CPR* Cardiopulmonary resuscitation; *ACLS* Advanced cardiac life support

14.2 Pharmacological Effects of Corticosteroids

Corticosteroids are a class of chemicals involved in a wide range of physiological processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior. The possible effect of exogenously administered steroids on cardiac arrest outcomes was already hypothesized in 1988. Still, there is no definitive evidence on their efficacy when given to cardiac arrest patients after ROSC.

The physiological effects of glucocorticoids can be summarized as follows:

1. Anti-inflammatory effects: Glucocorticoids inhibit inflammatory and allergic reactions by decreasing the production of interleukin (IL)-2 as well as the proliferation of T-lymphocytes, histamine, and serotonin release, and prostaglandin and leukotriene synthesis.
2. Renal effects: Glucocorticoids restore glomerular filtration rate and renal blood flow to normal following adrenalectomy; in addition, they facilitate free water excretion (clearance) and uric acid secretion.
3. Vascular effects: In pharmacological doses, cortisol enhances the vasopressor effect of norepinephrine. In the absence of cortisol, the vasopressor action of catecholamines is diminished, and hypotension ensues.
4. Stress adaptation: Corticosteroids allow mammals to adapt to various stresses in order to maintain homeostasis. Stress is associated with the activation of the hypothalamic–pituitary–adrenal axis.
5. Corticosteroids also have gastric, psychoneural, and antigrowth effects.
6. Metabolic effects: Glucocorticoids stimulate gluconeogenesis through: (a) increase in protein catabolism and decrease in protein synthesis, resulting in more amino acids being available to the liver for glyconeogenesis; (b) decrease in insulin sensitivity and glucose utilization in adipose tissue; and (c) increase in lipolysis, so as to offer more substrate for gluconeogenesis.

14.3 Retrospective Data on Steroids in Cardiac Arrest

The potential usefulness of steroids in cardiac arrest has been previously assessed in two retrospective studies. Grafton et al. [4] examined the effect of steroid treatment on the early neurological outcome and in-hospital survival of 458 consecutive patients admitted after out-of-hospital cardiac arrest. Two hundred and thirteen patients (47 %) received median doses of 24, 16, and 16 mg of dexamethasone or its equivalent on days 1, 2, and 3 post-ROSC, respectively; the reported median duration of treatment was 3.4 days, and 87 % of these patients received steroid treatment for one week or less. Of those receiving steroids, 128/213 (60 %) regained consciousness, and of those not receiving steroids, 150/245 (61 %) regained consciousness. There was no reported comparison of patient baseline characteristics, despite the fact that the use of steroids was nonrandomized. However, findings remained unchanged after using logistic regression to adjust for differences in potential effect modifiers between the two treatment groups. These factors were: witnessed or not witnessed cardiac arrest, use of epinephrine or norepinephrine during resuscitation, and motor examination findings, response of the pupils to light, presence of spontaneous eye movements, and blood glucose level on hospital admission. According to the authors, these results could not support any role of steroids in the treatment of global brain ischemia due to cardiac arrest.

One year later, an article published in JAMA [5], concluded that "The routine clinical practice of administering glucocorticoids after global brain ischemia is not justified." This was a retrospective analysis of prospectively collected data aimed at evaluating the efficacy of thiopental in global cerebral ischemia. The study included 262 initially comatose, cardiac arrest survivors, who made no purposeful response to pain after ROSC. These patients were divided into four groups which received either no glucocorticoids, or glucocorticoids at low doses (i.e., equivalent to 1–20 mg of dexamethasone), or glucocorticoids at medium doses (i.e., equivalent to 20–50 mg of dexamethasone), or glucocorticoids at high doses (i.e., equivalent to >70 mg of dexamethasone) within the first 8 h following ROSC. The paper did not report a comparison of the baseline characteristics of the four patient groups. Also, the glucocorticoid doses administered within 8–24 h post-ROSC were unknown. Furthermore, the extent of the protocolized use of post-ROSC hyperventilation (titrated to a $PaCO_2$ of 25–35 mmHg) was not compared among the four groups; hyperventilation may adversely affect cerebral blood flow and neurological outcome [6]. Finally, cardiac arrest due to noncardiac causes (an independent predictor of poor outcome [7]) was more frequent in the steroid-treated patients. In that study, neurological outcome was scored using a modification of the Glasgow–Pittsburgh Cerebral Performance Category Scale. Steroid-treated groups versus the "no steroid" group had no significant improvement in overall survival or neurological recovery [5].

14.4 Defining the Postcardiac Arrest Syndrome

ROSC after prolonged, complete, whole-body ischemia is an unnatural pathophysiological state created by successful cardiopulmonary resuscitation (CPR). In the early 1970s, Negovsky recognized that the pathology caused by complete, whole-body ischemia and reperfusion was unique in that it had a clearly definable cause, time course, and constellation of pathophysiological processes [8–10]. Negovsky named this state "post-resuscitation disease." Although appropriate at the time, the term "resuscitation" is now used more broadly to include treatment of various shock states in which circulation has not ceased. Moreover, the term "post-resuscitation" implies that the act of resuscitation has ended. Negovsky stated that "a second, more complex phase of resuscitation begins when patients regain spontaneous circulation after cardiac arrest (Fig. 14.2) [8]." Therefore, the term "postcardiac arrest syndrome" seems more appropriate.

The high mortality rate of patients who initially achieve ROSC after cardiac arrest can be attributed to a unique pathophysiological process that involves multiple organs. Although prolonged, whole-body ischemia initially causes global tissue and organ injury, additional damage occurs during and after reperfusion [11, 12]. The unique features of postcardiac arrest pathophysiology are often superimposed on the disease or injury that caused the cardiac arrest, as well as underlying comorbidities. Therapies that focus on individual organs may compromise other injured organ systems. The four key components of postcardiac arrest syndrome are (1) postcardiac arrest brain injury, (2) postcardiac arrest myocardial dysfunction, (3) ischemia/reperfusion-triggered, systemic inflammatory response, and (4) persistent underlying pathology [13].

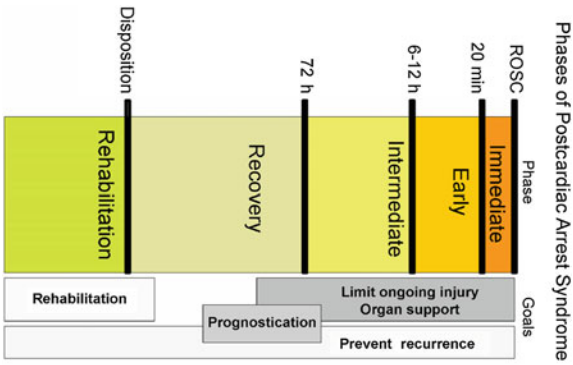


Fig. 14.2 The phases of the postcardiac arrest syndrome. Reproduced with permission from Ref. [13]

14.5 Postischemic Myocardial Dysfunction and Corticosteroids

Postcardiac arrest myocardial dysfunction contributes to the low survival rate after in-hospital and out-of-hospital cardiac arrest [14–16]. Laboratory and clinical evidence, however, indicates that this phenomenon is both responsive to therapy and reversible [16–21]. Immediately after ROSC, heart rate and blood pressure are extremely variable. It is important to recognize that normal or elevated heart rate and blood pressure immediately after ROSC can be caused by a transient increase in local myocardial and circulating catecholamine concentrations [22, 23]. Using an experimental model of coronary microembolization, Hori et al. [24] demonstrated that after a rapid (i.e., 5–10 min lasting) recovery from the immediate, microembolization-induced ischemic myocardial dysfunction, a progressive and more prolonged (i.e., lasting for approximately 4 days) contractile dysfunction develops in the presence of an unchanged regional myocardial blood flow [25]. This perfusion–contraction mismatch was associated with a local inflammatory response characterized by leukocyte infiltration [25]. In subsequent studies, a causal role for tumor necrosis factor (TNF) and sphingosine in this progressive contractile dysfunction was demonstrated [26, 27]. Interestingly, high-dose (i.e., 30 mg/kg) methylprednisolone, even when given after microembolization, prevented the progressive contractile dysfunction [28].

Glucocorticoids have been used for their anti-inflammatory action in the treatment of a wide variety of diseases [29]. More specifically, glucocorticoids attenuate leukocyte/endothelium interactions [30–33], as well as the generation and release of inflammatory cytokines and mediators [34–38]. Cardioprotective effects of glucocorticoids in the acute setting of myocardial ischemia/reperfusion have been shown experimentally with regard to structural and functional myocardial damage [39–45].

The inflammation of early myocardial ischemia is characterized by leukocyte infiltration [46, 47], a process involving the expression of L-selectin, CD11/CD18-complex, and adhesion molecules [48, 49]. Glucocorticoids suppress the expression of L-selectin and CD11/CD18 on leukocytes [32, 33], and the expression of endothelial leukocyte adhesion molecule-1 and the intercellular adhesion molecule-1 [30]. Glucocorticoids have previously been shown to inhibit the expression of mRNA of TNF in immunologically activated, rat, peritoneal mast cells [37], to suppress the production of TNF in the serum and the myocardium of lipopolysaccharide-stimulated rats [38], and to abolish the release of TNF into the serum of humans during cardiac surgery [36]. Glucocorticoids also attenuate the infiltration of TNF–producing macrophages/monocytes after coronary microembolization in pigs [50].

In the past, glucocorticoids have been used clinically for the treatment of acute myocardial infarction [51–53], but such treatment was abandoned because of their potentially deleterious, long-term effects on scar stability and aneurysm formation [54, 55]. However, results from chronically instrumented dogs suggest that anti-inflammatory treatment by a single dose of glucocorticoids in the presence of

small, patchy microembolization-induced infarcts exerts no adverse effects [28]. Furthermore, a more recent meta-analysis of human data from 11 controlled trials suggested a possible mortality benefit for corticosteroid treatment of myocardial infarction [56].

14.6 Postcardiac Arrest Systemic Inflammatory Response and Corticosteroids

The American Heart Association Guidelines 2010 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care state that the postcardiac arrest syndrome has similarities to septic shock [57, 58]. However, the efficacy of corticosteroids remains controversial in patients with sepsis [59–61]. The mechanisms underlying the postcardiac arrest syndrome involve a whole-body ischemia and reperfusion that triggers a systemic inflammatory response [58, 62]. Altogether, the high levels of circulating cytokines, the presence of endotoxin in plasma, and the dysregulated production of cytokines found in cardiac arrest patients resemble the immunological profile found in patients with sepsis [58].

The postcardiac arrest syndrome seems to be causally related to an early systemic inflammatory response, leading to an inflammatory imbalance [62, 63], and is also associated with an "endotoxin tolerance," as observed in severe sepsis [64]. Additional disturbances include activation of the coagulation cascade [65, 66], platelet activation with formation of thromboxane A2 [67], and an alteration of soluble E-selectin and P-selectin [63] have been described.

The postcardiac arrest syndrome can be temporally subdivided into four phases (Fig. 14.2) [62]: (1) Within the first 24-h post-arrest, a microcirculatory dysfunction from the multifocal hypoxia leads to rapid release of toxic enzymes and free radicals into the cerebrospinal fluid and blood; (2) over the next 1–3 days, cardiac and systemic functions improve, but intestinal permeability increases, predisposing the patient to sepsis and the multiple organ dysfunction syndrome; (3) during the subsequent days, a serious infection may occur causing rapid clinical deterioration; and (4) the patient either dies of a secondary complication or the primary disease that caused the cardiac arrest, or undergoes a frequently prolonged, partial or complete recovery.

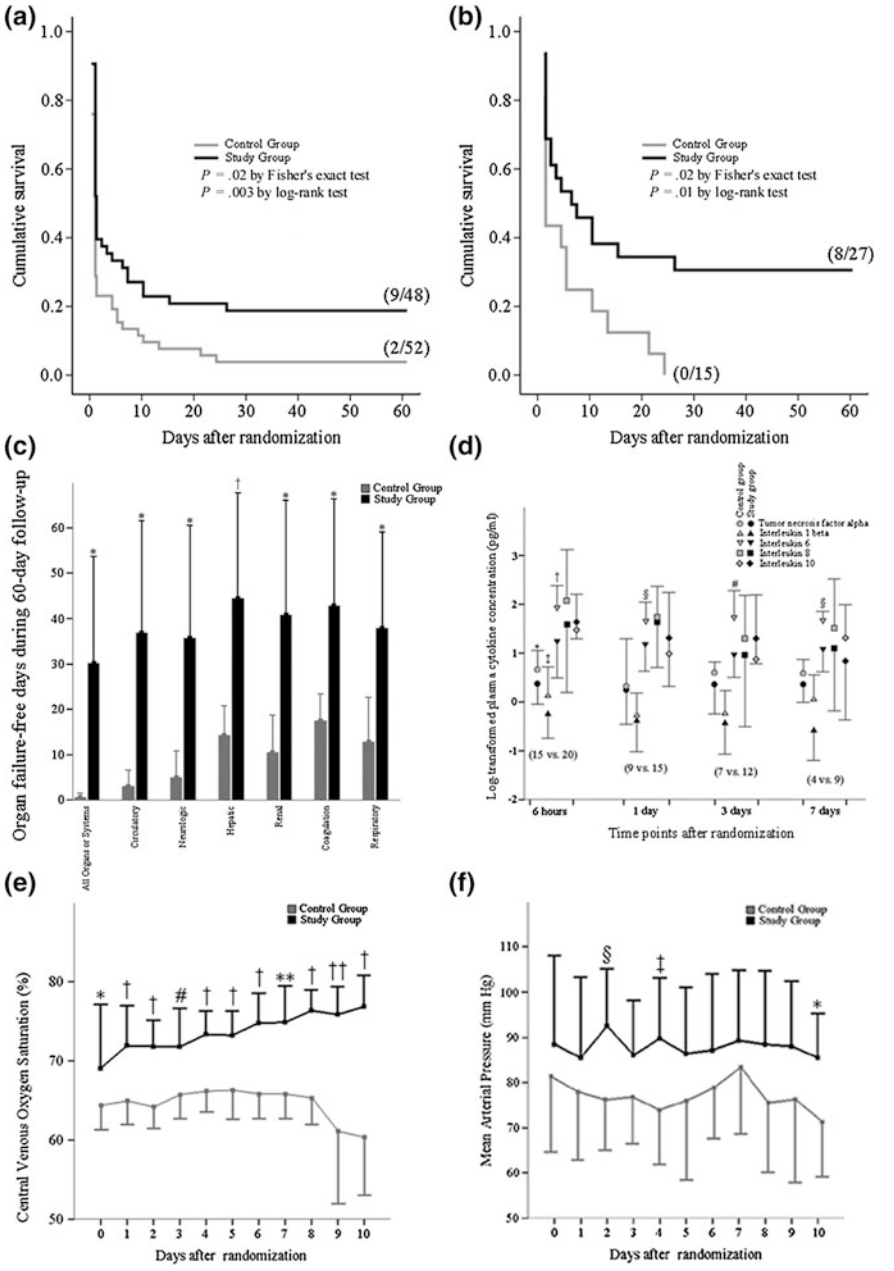
The Surviving Sepsis Campaign guidelines 2012 for the management of severe sepsis and septic shock suggest stress-dose hydrocortisone therapy (daily dose: 200 mg) only for patients who are poorly responsive to fluid and vasopressor therapy [68]. However, in cardiac arrest patients, treatment-refractory shock is a common post-ROSC complication [69]. Furthermore, post-resuscitation shock is frequently partly due to a post-arrest adrenal insufficiency or dysfunction [58, 62, 70], which in turn constitutes an independent predictor of mortality at 1 week after resuscitation [71]. In light of these facts, in our recently published, single-center (sample size: 100 patients), randomized, double-blind, placebo-controlled study of vasopressor-requiring, in-hospital cardiac arrest [69], we administered 40 mg of

methylprednisolone during CPR, and stress-dose hydrocortisone (300 mg/day for a maximum of 7 days followed by gradual taper) to patients fulfilling a clearly defined criterion for post-resuscitation shock. Our CPR intervention also included vasopressin (dose range: 20–100 IU) and epinephrine. The control group received standard, epinephrine-based CPR according to the contemporary guidelines for resuscitation. Intervention group results showed a combination of improved post-arrest hemodynamics and central venous oxygen saturation, post-arrest cytokine levels and organ/system function, and survival to hospital discharge (Fig. 14.3). Survival to hospital discharge was improved in the total intervention group (Fig. 14.3a) as well as in the subgroup of patients with post-resuscitation shock (Fig. 14.3b). Furthermore, multivariate Cox regression analysis showed that the assignment to the intervention group and completion of a full post-arrest course of hydrocortisone was associated with a hazard ratio of 0.15 (95 % confidence interval: 0.06–0.38, $P < 0.001$) for in-hospital death during follow-up. These results were consistent with a steroid-associated benefit in cardiac arrest. However, the combined nature of our intervention precluded a precise determination of the relative contribution of the steroids to the positive outcomes of the intervention group.

Another pilot (sample size: 100 patients), randomized, unblinded study of out-of-hospital cardiac arrest [72], showed improved rates of ROSC in its intervention group patients, who received a single dose of 100 mg of hydrocortisone during CPR. Interestingly, and consistently with prior findings [70], patients of the study's control arm with a serum cortisol level of more than 20 μg/dL had a ROSC rate of 43 %, as opposed to a ROSC rate of 25 % that was observed in controls with a serum cortisol level of less than 20 μg/dL.

14.7 Corticosteroids and Neuroprotection

To date, there is no published data showing that peri-arrest glucocorticoids are neuroptotective [73]. In the peri-arrest period, there is a multifactorial disruption of the blood–brain barrier (BBB), involving the enhanced production of nitric oxide, inflammatory cytokines, and vascular endothelial growth factor [74]. According to recent evidence, several of these mechanisms could constitute potential targets of corticosteroid treatment. Corticosteroids promote BBB integrity through their interaction with astrocytic cells, which results in upregulation of the endothelial tight junction proteins such as occludin and claudin-5 [75]. Glucocorticoids regulate the expression of leukocyte adhesion molecule genes in endothelial cells [76], and suppress the production of the pro-inflammatory cytokines [34–38, 77]. Methylprednisolone attenuates axonal changes (e.g., myelin fragmentation and presence of edematous vesicles), caused by experimental cerebral edema [78]. In addition, 17-beta estradiol suppresses the expression of inducible nitric oxide synthase and neuronal nitric oxide synthase, thus attenuating the BBB disruption after experimental, hypovolemic cardiac arrest [79]. However,


(a)
Cumulative survival
Control Group
Study Group
P = .02 by Fisher's exact test
P = .003 by log-rank test
(9/48)
(2/52)
Days after randomization
(b)
Cumulative survival
Control Group
Study Group
P = .02 by Fisher's exact test
P = .01 by log-rank test
(8/27)
(0/15)
Days after randomization
(c)
Organ failure-free days during 60-day follow-up
Control Group
Study Group
All Organ or Systems
Circulatory
Neurologic
Hepatic
Renal
Coagulation
Respiratory
(d)
Log-transformed plasma cytokine concentration (pg/ml)
Tumor necrosis factor alpha
Interleukin 1 beta
Interleukin 6
Interleukin 8
Interleukin 10
(15 vs. 20)
(9 vs. 15)
(7 vs. 12)
(4 vs. 9)
6 hours
1 day
3 days
7 days
Time points after randomization
(e)
Central Venous Oxygen Saturation (%)
Control Group
Study Group
Days after randomization
(f)
Mean Arterial Pressure (mm Hg)
Control Group
Study Group
Days after randomization

◀ **Fig. 14.3** Main results of patient follow-up. Reproduced with permission from Ref. [69]. Study group denotes intervention group. **a**, **b** Probability of survival to day 60 postrandomization, which was identical to survival to hospital discharge, in all 100 patients (**a**) and in the 42 patients with post-resuscitation shock (**b**). Parentheses, survivors/total number of patients. **c** Organ failure-free days in patients who completed a full course of hydrocortisone ($n = 12$) or saline-placebo ($n = 6$) according to protocol. Bars, mean; Error-bars, standard deviation; *, $P = 0.001$; †, $P < 0.001$. **d** Plasma-cytokines in post-resuscitation shock. Parentheses, number of controls versus number of study-group patients; Symbols, mean; Error-bars, standard deviation; *, $P = 0.04$; †, $P = 0.003$; §, $P = 0.02$; #, $P = 0.01$; ‡, $P = 0.06$. **e**, **f** Central-venous oxygen saturation (**e**) and mean arterial pressure (**f**) in post-resuscitation shock. Dots, mean; Error-bars, standard deviation. *, $P = 0.03$; †, $P < 0.001$; §, $P = 0.006$; #, $P = 0.005$; ‡, $P = 0.01$; **, $P = 0.002$; ††, $P = 0.04$

during the course of ischemic insults, insensitivity to glucocorticoids ensues, due to proteasome-induced degradation of the glucocorticoid receptor [80, 81]. This suggests that the inhibition of the proteasomal degradation pathway may constitute a prerequisite for the glucocorticoid-associated preservation of BBB integrity [80, 81]. Consequently, in cardiac arrest, it is still highly uncertain whether peri-arrest and/or post-arrest hydrocortisone can directly confer neuroprotection.

14.8 Conclusions

Preceding retrospective studies with inherent methodological limitations do not support the use of low-dose corticosteroids during and after CPR. However, more recent laboratory data and clinical results are consistent with a possible, low-dose corticosteroid-associated, benefit in cardiac arrest, especially in patients with post-resuscitation shock. Such potential benefit can be explained mainly by the hemodynamic and anti-inflammatory effects of hydrocortisone, as a direct neuroprotective effect seems rather unlikely. Controversies and unclear mechanisms of hydrocortisone action and possible efficacy should be addressed by a large, multicenter, randomized, placebo-controlled evaluation of stress-dose hydrocortisone in cardiac arrest.

14.9 Financial and Competing Interests Disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or a financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance has been utilized in the production of this manuscript.

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