The Resuscitation Outcome*

Revisit the Story of the Stony Heart

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Postresuscitation syndrome is a state of myocardial dysfunction after the restoration of circulation by successful resuscitation. Despite several advances in the field of resuscitation, the management of out-of-hospital cardiac arrest is still suboptimal. The high fatality rate shortly after successful resuscitation is mainly related to postresuscitation myocardial dysfunction. Postresuscitation myocardial stunning is reversible, while stony heart is irreversible due to prolonged unsuccessful resuscitation. This article reviews most of the published articles concerning the causes, mechanism, pathophysiology, and the updated trials for management of postresuscitation myocardial dysfunction. Further studies are warranted to highlight postresuscitation disease and its hemodynamic sequences and then to intervene according to the different phases of cardiac arrest. By modifying the conventional modalities of resuscitation together with new promising agents, the rescuers will be able to salvage the jeopardized postresuscitation myocardium and prevent its progression to the dismal stony heart. Community awareness and staff education are crucial to shorten resuscitation time and improve short-term and long-term outcomes. There is an urgent need to revise the guidelines for cardiopulmonary resuscitation in community setting, but how? It is a matter of where and when it is of enough value to be efficacious and cost-effective.

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Abbreviations: AED = automated external defibrillator; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CPR = cardiopulmonary resuscitation; KATP = adenosine triphosphate-dependent potassium; LV = left ventricle/ventricular; NHE-1 = sodium-hydrogen exchanger isoform-1; NOS = nitric oxide synthase; PAD = public access defibrillation; PDE IIIi = phosphodiesterase III inhibitor; PEA = pulseless electrical activity; SCD = sudden cardiac death; VF = ventricular fibrillation

The postresuscitation period is well recognized as the main predictor of resuscitation outcome. Early defibrillation is the most important and effective variable in this period. Successful cardiopulmonary resuscitation (CPR) is not a momentary event, and the long-term outcome should be the aim. Twenty to 40% of patients who had cardiac arrest are initially resuscitated, but only 10% survive to hospital discharge. There is marked but reversible form of systolic and diastolic myocardial dysfunction together with life-threatening ventricular arrhythmias that compromise postresuscitation survival, with a high fatality rate in the early hours and days after successful resuscitation. This fatal outcome of victims after initially successful resuscitation for cardiac arrest has been attributed to global myocardial ischemia during the cardiac arrest and the adverse effects of reperfusion. Successful CPR is complicated with a stunned myocardium, while failed or prolonged CPR is complicated with a stony myocardium, which is the worst form of myocardial dysfunction. Awareness of the pathophysiology before, during, and early after restoration of the circulation is of crucial importance to improve the outcomes of CPR.[1–4] Successful treatment of post-CPR myocardial failure could save approximately 25,000 patients per year.

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Outcome of Resuscitation

Incidence rates of sudden cardiac death (SCD) ranging from 0.36 to 1.28 per 1,000 inhabitants per year have been reported.[5,6] Twenty-one percent of all deaths were sudden and unexpected in men, and 14.5% were sudden and unexpected in women. Eighty percent of out-of-hospital cases may occur at home, and approximately 15% occur on the street or in a public place, while 40% of SCDs are unwitnessed. Before the introduction of automated external defibrillators (AEDs), only 15% of all out-of-hospital cardiac arrest victims had restoration of spontaneous circulation and reached the hospital alive. Of those, only 50% survived to hospital discharge. Considering only patients presenting with ventricular fibrillation (VF), survival to discharge is approximately double.[7] CPR itself yields a functional survival rate of only 1.4 to 5%.

In the Brain Resuscitation Clinical Trial I and II,[8,9] a total of 778 patients were successfully resuscitated; 70% of them died within the first 72 h, while 65% died within 1 week. A sign of postresuscitation myocardial dysfunction before death in the form of recurrent cardiac arrest, marked hypotension, or shock has been noted in > 50% of victims.[5,6,8–10] In other multicenter clinical studies,[8,9,11] 60% of 407 resuscitated patients died within 72 h. Hypotension and ventricular arrhythmias were identified as predominant causes of death, and only 4.5% of patients were ultimately discharged alive from the hospital. Two clinical studies[12–13] have reported serial measurements of indexes of cardiac function after resuscitation and indicated that the initial lower ejection fraction after CPR is a predictor for lower cardiac index, which in turn presages the development of multiorgan failure and mortality in the next 24 h.

Factors Affecting the Outcome of Resuscitation

The results of CPR are influenced not only by the resuscitation efforts but also by the conditions before initiation of CPR. The causes of death after resuscitation include CNS damage in one third of cases, refractory myocardial damage in another third, and sepsis and other complications in the last third. In two meta-analysis studies[14–16] of 4,937 cases of cardiopulmonary arrest, the poor outcome following in-hospital arrest was related to multiple variables: prearrest variables (*ie*, hypotension, renal failure, pneumonia, and cancer); intra-arrest variables (*ie*, duration of arrest [> 15 min]); unwitnessed arrests; initial rhythm other than ventricular tachyarrhythmia; multiple ECG events; increasing doses of epinephrine; resuscitations between 12 midnight and 6:00 AM; and postarrest variables, such as decreased level of consciousness over 24 h, new-onset azotemia, recurrent cardiopulmonary arrest, and persistent hypotension.

Specific therapeutic interventions applied in each phase of cardiac arrest are critical for a successful outcome Three phases have been identified during cardiac arrest. The first is the electrical phase, which lasts approximately 5 min, during which defibrillation is the priority. The use of AEDs within 3 min following the onset of VF resulted in the highest ever reported survival of 70%. Survival from VF cardiac arrest declines approximately 7 to 10% for each minute without defibrillation.[17] The second phase is hemodynamic phase, which lasts from 4 to 10 min. During this time, circulatory support using chest compression is the priority. During the hemodynamic phase, the left ventricle (LV) becomes empty as blood is shifted to the right side. The third phase is the metabolic phase, when drugs and hypothermia can be used. In the latter two phases of cardiac arrest, perfusion is critical in maintaining coronary perfusion pressure and is vital to survival. The use of an AED can be harmful in the last two phases.[18–19] Electrical shock in patients with prolonged VF result in defibrillation not to a perfusing rhythm but to pulseless electrical activity (PEA).[20] Thus, the methodology of CPR and its application according to the appropriate phase of cardiac arrest play pivotal role in the fate of the postresuscitation myocardial function.

Impact of Ischemia-Reperfusion Injury

Ischemia-reperfusion injury is thought to be due to the generation of oxygen-derived free radicals such as superoxide and hydroxyl radicals. Such free radicals lead to lipid peroxidation, cellular dysfunction, and stunning of the myocardium. Numerous studies have implicated the nitric oxide-peroxynitrite pathway in ischemia-reperfusion injury. Reperfusion and reoxygenating could play an important precipitating role in postresuscitation myocardial dysfunction.[21–25]

Postresuscitation Disease

Postresuscitation disease is a specific pathophysiologic state of vital organ systems early after ischemic anoxia. Adrie et al[26,27] hypothesized that postresuscitation disease may be related to an early systemic inflammatory response, leading to an exacerbation of the inflammatory balance, and may possibly be associated with an "endotoxin tolerance." Postresuscitation disease is similar to that seen in severe sepsis, as it characterizes by high levels of circulating cytokines and adhesion molecules, the presence of plasma endotoxin, and dysregulated leukocyte production of cytokines. 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. The stress-induced proinflammatory cytokines, particularly tumor necrosis factor-α and interleukin-1β, are known to depress myocardial function. Tumor necrosis factor-α and interleukin-1β, synthesized and released in response to the stress of global ischemia accompanying cardiac arrest, play a role in development of postresuscitation LV dysfunction as well.[26–28] Detection of high levels of endogenous vasopressin and catecholamines during resuscitation has therapeutic and prognostic implications.[29–30]

Postresuscitation Syndrome

Postresuscitation syndrome is a state of myocardial dysfunction after the restoration of circulation by successful resuscitation. It manifests by increased cardiac filling pressures, decreased cardiac index, and a decrease in both systolic and diastolic function. Severe but temporary LV systolic and diastolic dysfunction may follow 10 to 15 min of untreated cardiac arrest and successful resuscitation. The dramatically global nature of this systolic dysfunction after resuscitation has been demonstrated with echocardiography, as well as ventriculography, and revealed decrease in ejection fraction, a decrease in fractional shortening, a decrease in the rate of rise of LV pressure, a decrease in peak systolic LV pressure/end-systolic volume ratio, and a rightward shift in the pressure/volume relationship[4,11]

Stunned Myocardium

Stunned myocardium is prolonged postischemic myocardial dysfunction with eventual return of normal contractile activity.[31] Stunning is now thought to occur in several clinical situations, including delayed recovery from effort angina, unstable angina, early thrombolytic reperfusion, ischemic cardioplegia, cardiac transplantation, coronary angioplasty, and cardiac arrest. The concept of ischemic contracture of the myocardium is associated with myocardial stunning. The same concept may be applicable to the global myocardial ischemia of cardiac arrest. Augmented crossbridging between actin and myosin followed depletion of high-energy phosphates explains the severity of myocardial stiffness.

During ischemia, there is a reduction in both creatine phosphate and adenosine triphosphate (ATP). With reperfusion, there is immediate restoration of the normal creatine phosphate level, while ATP takes several days to return to normal; this depletion of the total adenine nucleotide pool leads to prolonged depression of myocardial contractility. The other possible mechanisms of myocardial stunning include alteration in sarcoplasmic calcium ATP and calcium metabolism, up-regulation of the heat shock protein, and generation of oxygen-free radicals. A major hypothesis with significant experimental support is that enhanced oxidative stress is a critical component in the pathophysiology of stunning.[32] Myocardial stunning after respiratory arrest has been followed by full recovery occurred within few days after successful resuscitation. Hence, LV pressures, cardiac index, and hemodynamically measured isovolumic relaxation time all confirmed LV systolic and diastolic dysfunction.[2,33]

According to Kern et al,[2,34] myocardial stunning includes the persistence of LV dysfunction after the return of normal myocardial blood flow, and myocardial blood flow might be unchanged between baseline levels and that found at 5 h after resuscitation, even though LV ejection fraction remained markedly decreased by 5 h. These data convincingly show that this phenomenon of postresuscitation myocardial dysfunction is an example of acute but reversible heart failure, and thus aggressive support is indicated during the first 48 to 72 h.

Stony Heart

Ischemic contracture refers to the progressive myocardial wall thickening with reductions in ventricular cavity that results from severe ischemia. Its onset is associated with decreases in ATP to levels $< 10\%$ of normal. Ischemic contracture of varying severity has been reported during cardiac arrest to compromise resuscitability in animal models and in human victims of cardiac arrest. Ischemic contracture occurred with essentially no changes in end-of-chest-relaxation LV pressures, confirming reductions in myocardial compliance. Stony heart is a severe form of ischemic contracture in which a progressive impairment in diastolic function during CPR precedes evolution of the "stone heart" after failure of or prolonged CPR.[35–37]

Klouche et al[37] described the term *stone heart* in animals. They induced VF in 40 pigs; after 4 min, 7 min, or 10 min of untreated VF, electrical defibrillation was attempted. Failing to reverse VF in each instance, precordial compression at a rate of 80/min was begun coincident with mechanical ventilation. The result showed that significantly greater coronary perfusion pressures were generated with the 4 min of untreated cardiac arrest, while progressive reductions in LV diastolic and stroke volume and increases in LV free-wall thickness were documented with increasing duration of untreated VF. A stone heart was confirmed at autopsy and correlated with the echocardiographic in each animal with failed resuscitative efforts. Myocardial stiffness, in turn, accounted for decreased effectiveness of chest compression for producing forward blood flow during CPR and perpetuating a vicious circle.[37]

Role of the Initial Rhythm

The most common initial arrhythmias encountered in cases of out-of-hospital SCDs are VF or ventricular tachycardia. However, nonventricular rhythms including PEA and asystole are reported with increasing frequency as the first ECG findings in out-of-hospital SCDs. This rhythm group now appears to represent the majority of patients in whom out-of-hospital resuscitation is attempted. In most reports, the rate of survival when PEA or asystole is the initial documented cardiac arrest rhythm is poor and approximates 2%.[10,39–42] It is likely that VF is the cause of 60 to 80% of cardiac arrests, while asystole results in 20 to 40%.[43,44] PEA may be found in up to 10% of patients with cardiac arrest. A number of theories have been proposed to explain the apparent refractoriness of asystole to resuscitation attempts, including impairment of the automaticity of the sinus node, malfunction of related conduction pathways secondary to ischemia, failure of neurogenic innervation of the heart, and failure of reflex sympathetic performance. It is clear that progressive ischemia and acidosis are always present.[45] Countershock of prolonged VF is followed by secondary PEA or asystole in approximately 60% of patients. Only 0 to 2% of postshock PEA and asystole patients survive to be discharged from the hospital.[46,47] Patients found in primary PEA or asystole at the time of resuscitative efforts have initially a significantly higher rate of restoration of spontaneous circulation and survival to hospital admission than for patients found in VF with PEA or asystole after countershock. In rare instances, low-amplitude VF can "masquerade" as asystole; laboratory and clinical studies[48–51] indicate that low-amplitude VF rarely responds favorably to countershock.

Impact of Fibrillation

During VF, the normal balance of myocardial energy supply and demand is disrupted because the demand of the myocardium for energy exceeds what is available from a reserve of high-energy phosphates and from anaerobic glycolysis. Consequently, the net supply of ATP available to the myocyte decreases to critical level. Decrease in myocardial tissue ATP during ischemia is correlated with the severity of myocardial injury, and therefore it is a predictive of myocytes survival when coronary perfusion is restored.[52–54]

Patients with VF suffer a complex set of insults that may include defibrillation, ischemia, and even tissue infarction. It is worth remembering that the classic concept of myocardial stunning is a consequence of ischemia, not defibrillation. However the final lesion in stunning is a reduction in the myofilament contractile response to increases in intracellular calcium; a similar lesion underlies mechanical dysfunction after successful defibrillation (independent of the means of defibrillation) has been reported.[55]

Effect of Defibrillation

Electrical shocks that defibrillate hearts successfully also produce myocardial injury, and this injury increases with the higher energy shocks. The harmful effect has been shown if defibrillation administered in the second and third phases during cardiac arrest. The electrochemical activity of the arrhythmia itself may, in the absence of ischemia, contribute to excitation-contraction uncoupling via intracellular calcium overload. Electrical countershocks may potentiate this effect and have furthermore been linked to the dose-dependent release of free radicals and to waveform-specific effects on mitochondrial function and oxidative metabolism, which might aggravate the postresuscitation stunning.[56–58]

High-energy defibrillator produces more severe LV dysfunction, while fixed low-energy biphasic waveform defibrillation significantly reduces the severity of postresuscitation myocardial dysfunction compared with an escalating monophasic energy defibrillator. Defibrillators with 4 J/kg produce significantly less postresuscitation dysfunction than either 20 J/kg or 40 J/kg, and the maximum survival and minimum myocardial dysfunction were observed with the low-capacitance 150-J waveform. It has been shown that diastolic function is more impaired than systolic function for both waveform types, with more prominent filling impairments after monophasic countershocks persisting for up to 15 min, while the systolic function was much better with biphasic shocks.[58–60] By lowering the defibrillation threshold, biphasic waveform defibrillation will improve survival after prolonged VF arrest.[59–61]

Chest Compression and Myocardial Perfusion

The weakest links in the chain of survival after out-of-hospital cardiac arrest due to VF are the lack of bystander-initiated basic CPR and the delay in defibrillation. Since the coronary and cerebral vessels are maximally dilated during cardiac arrest, the main factor in myocardial perfusion during basic CPR is the coronary perfusion pressure, which depends on the diastolic pressure that created during the release phase of chest compression. The cerebral perfusion pressure is related to the systolic pressure created during the chest compression phase of CPR. The perfusion pressure falls every time chest compressions are interrupted for assisted ventilation, and it takes time to build up again once chest compressions are reinitiated.[62] Accordingly, with a ratio of 15 compressions to two breaths, the highest perfusion pressures are present for less than half the time. Starting with chest compressions in the hemodynamic phase can attain a survival of 20% compared to 4% if during this phase electrical shock is administered first and followed by chest compressions.[63] Hallstrom et al[64] confirmed that in cases of witnessed sudden cardiac arrest with a nonrespiratory cause, CPR by chest compression alone is as good as, and possibly better, than standard CPR by compression plus ventilation. Wik et al[65] agreed that CPR first prior to defibrillation offered no advantage in improving outcomes for some cases or patients with ambulance response times < 5 min. However, the patients with VF and ambulance response intervals > 5 min had better outcomes with CPR first before defibrillation was attempted.[65] Interruptions of precordial compression for rhythm analyses that exceed 15 s before each shock compromise the outcome of CPR and increase the severity of postresuscitation myocardial dysfunction.[66]

Adrenergic Vasopressor During CPR

Adrenergic vasopressor agents are employed to increase peripheral vascular resistance to increase aortic diastolic pressure and, consequently, coronary perfusion pressure and myocardial blood flow. Epinephrine initially doubles coronary blood flow.[66] However, intense vasoconstrictor itself improves coronary perfusion pressure but at the expense of the outcome; the postresuscitation stunned LV may be unable to tolerate the substantially increased systemic vascular resistance.[68] The β- and, to a lesser extent, the α_1-adrenergic inotropic and chronotropic actions increase oxygen consumption of the fibrillating ventricles.

Experimentally, epinephrine-treated animals require a large number of direct-current shocks, which will increase the severity of myocardial ischemia. The β-adrenergic action of epinephrine in myocardial resuscitation has undesirable effects, as it increases the likelihood of reentrant and ectopic ventricular dysrhythmias, shortens the ventricular relaxation time, induces pulmonary ventilation/perfusion defects during CPR, increases myocardial lactate content, decreases myocardial ATP content, and is independently associated with unfavorable neurologic function after CPR.[67,69,70] The results of four clinical studies[71–74] in which high vs conventional doses were compared showed that the general rate of recovery of spontaneous circulation was increased as greater doses were used (0.07 to 0.20 mg/kg), but there was no significant statistical difference in terms of increasing the rate of survival or hospital discharge. Berg et al[74] disagreed and reported that high-dose epinephrine even with a β-blocker during CPR resulted in worse outcome than standard-dose epinephrine with or without a β-blocker.

Buffer Therapy

The combination of buffer therapy with standard adrenergic vasoconstrictors during CPR results in greater impairment of postresuscitation myocardial dysfunction and decrease in survival (Table 1). Bleske et al[76] investigated the effect of sodium bicarbonate vs normal saline solution on the vasopressor effect of epinephrine after 10 min of untreated VF; they observed no significant differences in aortic systolic, diastolic, and coronary perfusion pressure or in the success of resuscitation between animals treated with sodium bicarbonate or saline solution, and even no hemodynamic benefit followed increases in the dose of sodium bicarbonate. Increases in blood pH are more likely to further increase myocardial oxygen requirements of the fibrillated heart and increase the severity of global ischemic myocardial injury. Patients with acidemia had a significantly greater pressor response to epinephrine than patients with alkalemia.[77,78] However, Sun et al[79] proved that the buffer agents in combination with adrenergic vasopressor failed to increase the pressor response to epinephrine; to the contrary, it compromised postresuscitation myocardial function and survival by increasing the myocardial oxygen requirements and intensifying myocardial ischemia.

Duration of Cardiac Arrest

The most significant factor for developing postresuscitation myocardial dysfunction is a prolonged resuscitation effort. The LV ejection fraction and pulmonary artery wedge pressure were significantly worse after resuscitation after 15 min of VF compared with only 10 min of VF. Progressive impairment in diastolic function will end with a stone heart after prolonged intervals of cardiac arrest. The University of Arizona Resuscitation Research Group has been investigating postresuscitation myocardial dys-

Table 1—*Variables Affect the Outcomes of Resuscitation Efforts**

Variables	Advantages	Disadvantages
Epinephrine	↑ peripheral vascular resistance; ↑ aortic diastolic pressure; ↑ coronary perfusion pressure; ↑ myocardial blood flow	↑ oxygen consumption of the fibrillating ventricles; intense vasoconstrictor itself may →↑ myocardial dysfunction; ↑ the likelihood of reentrant and ventricular ectopics; shortens the ventricular relaxation time; ↑ pulmonary ventilation/perfusion defects during CPR; ↑ myocardial lactate content and ↓ myocardial ATP content; requires a large number of direct-current shocks
Vasopressin	Induces higher coronary perfusion pressures; maintains better coronary and cerebral perfusion; alternating doses with epinephrine are beneficial in asystole or prolonged CPR	Intense vasoconstrictor may be not tolerated by stunned myocardium; arrhythmia, ↑ liver enzymes, ↓ platelets; bowel ischemia; costly
Short-acting β-blockers	Counteract harmful effect of exogenous epinephrine; abolish cardiotoxicity of endogenous catecholamines	Need more further studies
Buffer therapy	Maintain sufficient alveolar ventilation; only of value in resistant VF/asystole due electrolyte imbalance	↑ myocardial oxygen requirements of the fibrillated heart; ↑ the severity of global ischemic myocardial injury; inactivate administered catecholamines
Selective PDE III	↑ intracellular cAMP in cardiac cells and ↑ contractility; decrease coronary and peripheral vascular resistance; are not catecholamine-dependent →↓ the degree of LV dysfunction; ↓ incidence of refractory postshock PEA	Need more studies
Dobutamine	Enhance LV systolic function and improves LV diastolic relaxation; ↑ cAMP levels in the cardiac myocytes	Arrhythmogenic
KATP openers	Induce preconditioning →; ↓↓ voltage requirement for successful defibrillation; ↓ severity of postresuscitation myocardial dysfunction	Need more studies
Sodium-hydrogen exchanger	Improve the hemodynamic efficacy of chest compression; prevent recurrent VF; lessen postresuscitation myocardial dysfunction	Need more studies
δ-opioid receptor agonist	Pharmacologic hibernation; minimizes global ischemic injury during CPR	Need more studies
Free radicals inhibitors	↓ coronary sinus free radical concentration; abolish accumulation of the peroxynitration product; reduce reperfusion injury	Need more studies
Intracellular calcium overload		↓ calcium responsiveness of the myofilaments; → postfibrillatory myocardial dysfunction
Therapeutic hypothermia	↓ many of the chemical reactions associated with reperfusion injury, *ie* free radical production, excitatory amino acid release, and calcium shifts	Induce arrhythmias, infection, and coagulopathy
Chest compression	Increase coronary perfusion pressure; essential in the hemodynamic phase of arrest	If interrupted →↓ coronary perfusion
Fixed low-energy biphasic waveform defibrillator	Essential in the first phase of arrest; ↓ defibrillation thresholds; shorten resuscitation times and ↓ LV dysfunction	May be harmful in the second and third phase of arrest
Shorten the time: educate the community and use PAD	Major contributors to survival of adult victims of sudden cardiac arrest; PADs are inexpensive, self-instructional, easy to operate, and automatic, requiring no diagnostic ability; improve LV function	
Monophasic and escalated countershock		→ excitation-contraction uncoupling via intracellular calcium overload, more prominent filling impairments; produces more severe LV dysfunction
Prolonged CPR		LV ejection fraction and pulmonary capillary wedge pressure were significantly worse; will lead to stone heart, multiorgan failure
Brain death		Induce autonomic storm →↑ in myocardial interstitial adenosine and lactate concentrations → imbalance between oxygen consumption and oxygen delivery; unwanted outcome

*↑ = increase; ↓ = decrease; → = lead to; ↓↓ = marked decrease; →↓ = negatively affect; →↑ = lead to increase.

function with invasive and noninvasive measurements of LV before and after 10 min and 15 min of untreated cardiac arrest. After 10 min of untreated VF, maximal dysfunction was seen at 6 h with partial resolution by 24 h and full recovery by 48 h, indicating that postresuscitation myocardial dysfunction is a true stunning phenomenon. After 15 min of VF, no data could be obtained at 24 h because all such subjects died overnight. Such data suggest that transient LV failure after resuscitation can be life threatening, and resuscitation should not be delayed or prolonged to avoid the stony irreversible stage.[2,37,80]

Brain Death and Postresuscitation Outcomes

Brain death leads to a series of pathophysiologic changes with deleterious consequences on cardiac function. There is massive but transient release of circulating catecholamines associated with a sustained increase in myocardial norepinephrine and neuropeptide Y directly released from cardiac sympathetic nerve endings. This will result in a striking increase in myocardial oxygen demand as estimated by the increase in the rate-pressure product.[81,82]

The autonomic storm that might switch myocardial metabolism from an aerobic to anaerobic pattern is due to the coronary vasoconstrictor effect of norepinephrine and neuropeptide Y. Increased oxygen demand in parallel with impaired coronary reserve results in functional myocardial ischemia that contribute to the myocardial dysfunction observed after brain death. There is an association between brain death and an increase in myocardial interstitial adenosine and lactate concentrations, as well as with myocardial dysfunction; all were attenuated by concomitant β-blocker, suggesting an imbalance between oxygen consumption and oxygen delivery as a possible cause of myocardial dysfunction after brain death.[81,83] Temporary delay in the circulation during cardiac arrest will cause brain death, which in its turn will compromise the myocardium during its way toward recovery.

Prevention of Postresuscitation Myocardial Dysfunction

Urgency to revise the CPR guidelines is needed but should be cautiously commenced, as the outcome has not yet dramatically changed despite advances in CPR techniques. Understanding the concept of postresuscitation disease will minimize the proinflammatory cascade and improves its hemodynamic status. This will highlight the mechanism of postresuscitation myocardial dysfunction and address the importance of new management modalities for its prevention and treatment. All efforts should aim to shorten the time of CPR and to be coincident with the relevant phase of the cardiac arrest.

Inotropes and Vasopressors

The minimum coronary perfusion pressure and myocardial blood flow needed to achieve successful defibrillation are 15 mm Hg and 15 to 20 mL/min per 100 g, respectively. Standard CPR techniques cannot meet these minimum requirements in the absence of pressor agents.[84]

Dobutamine is the only drug that has been systematically evaluated in animal models of cardiac arrest and resuscitation. Optimally, dobutamine should be administered within 15 min of successful resuscitation and at rate of 5 μg/kg/min. This will successfully treat postresuscitation LV systolic and diastolic dysfunction without adversely affecting myocardial oxygen consumption. Dobutamine improves diastolic relaxation of the LV through the same mechanism by which it improves systolic function, mainly by increasing cyclic adenosine monophosphate (cAMP) levels in the cardiac myocytes. Dobutamine is superior to the intra-aortic balloon pump for treatment of postresuscitation LV systolic and diastolic dysfunction, especially if there is no antecedent coronary artery disease.[85,86]

Epinephrine Alternatives

Epinephrine still is the mainstay in advanced cardiac life support. However, it has been shown to significantly worsen postresuscitation myocardial dysfunction, chiefly from its β-adrenergic effect during CPR. Efforts are going on to alleviate this harm either by adding β-blockers or by replacing them with more selective agents or by different vasopressors

Selective α_2-Adrenergic Agonists: Sun et al[87] reported that α-methylnorepinephrine was as effective as epinephrine for initial cardiac resuscitation but provided strikingly better postresuscitation myocardial function and survival.

Short-Acting β-Blockers: To counteract the harmful myocardial injury and increased metabolic demand due to epinephrine, two studies[67,88] suggested that the administration of a short-acting $[\beta]_1$-adrenergic blocking agent after prolonged VF improves the success of initial resuscitation, minimizes postresuscitation myocardial contractile impairment, and prolongs postresuscitation survival. Myocardial interstitial catecholamine levels are greatly elevated immediately after long-duration VF, defibrillation, and reperfusion. This high level of endogenous catecholamines is cardiotoxic. Therefore, the short-acting β-antagonist esmolol administered at reperfusion would protect against this catecholamine surge and improve survival after prolonged VF.[30]

Vasopressin: Endogenous vasopressin levels were found to be higher in survivors of cardiac arrest than in patients who died, suggesting that vasopressin could be beneficial in cardiac arrest.[29] Experimentally, vasopressin leads to significantly higher coronary perfusion pressures and maintained better oxygen delivery to the brain than did epinephrine. The recovery rate was significantly higher in animals treated with vasopressin than in those treated with epinephrine. Vasopressin has better activity in the acidemic environment; therefore, after prolonged arrest, the pressor effect of catecholamines is lowered and with vasopressin it is maintained.[89] Wenzel et al[90,91] compared vasopressin and epinephrine in out-of-hospital CPR and recommended the administration of 1 mg of epinephrine, followed alternately by 40 IU of vasopressin and 1 mg of epinephrine every 3 min in adult cardiac arrest victims regardless of the initial ECG rhythm to improve the outcome of CPR. Vasopressin followed by epinephrine may be more effective than epinephrine alone in the treatment of refractory cardiac arrest or asystole. On the contrary, a meta-analysis of five randomized controlled trials showed no clear advantage of vasopressin over epinephrine in the treatment of cardiac arrest. Deterioration of postresuscitation ventricular function early after resuscitation may be noticed after vasopressin but did not compromise 24-h outcome. Including vasopressin in the new guideline of CPR is still a debatable issue.[90–92]

Selective Phosphodiesterase III Inhibitors: Selective phosphodiesterase III inhibitors (PDE IIIis) elevate intracellular cAMP in cardiac cells and increase contractility. The increase in contractility has been ascribed to enhanced sarcolemmal entry of calcium into the cell, increased release and uptake of calcium by the sarcoplasmic reticulum, modulation of calcium-troponin interactions, and decrease of coronary and peripheral vascular resistance. The unique properties of PDE IIIis are not catecholamine dependent and suggest that such agents might be beneficial in the management of postresuscitation ventricular dysfunction. Milrinone, a selective PDE IIIi administered in a standard mid-range dose, can lessen the degree of LV dysfunction occurring within 60 min after resuscitation. It also appears to decrease the incidence of refractory postshock PEA.[93,94]

Induction of Preconditioning

The term *ischemic preconditioning* means that myocytes adapt to repetitive ischemic insults and are therefore protected against severe ischemic insults and cell death. Preconditioning essentially eliminates postresuscitation ventricular dysrhythmias. It is more likely that preconditioning improves myocardial mechanical function and mitigates postischemic arrhythmias by mechanisms other than infarction reduction.

ATP-Dependent Potassium Channel Openers: ATP-dependent potassium (KATP) channel openers are a structurally diverse class of agents that, among other activities, protect ischemic myocardial tissue. The pharmacologic opening of the KATP channel during cardiac resuscitation mimics the myocardial protective effects of ischemic preconditioning, and this may provide a new option for myocardial preservation during the global myocardial ischemia of cardiac arrest. Preconditioning either electrically by episodes of short duration VF or pharmacologically by KATP openers significantly reduces postresuscitation dysfunction and increases survival by reduction of voltage requirement for successful defibrillation, the incidence of postresuscitation ventricular ectopic beats, the severity of postresuscitation myocardial dysfunction, and postresuscitation fatal outcomes. Norepinephrine also may confer delayed preconditioning against myocardial stunning via an α_1-adrenoceptor–mediated pathway, but this norepinephrine-mediated preconditioning involves a beneficial effect toward stunning at the expense of a higher rate of ventricular arrhythmia.[95–97]

Induction of Hibernation

Given that hibernation is a state of energy conservation and is reproducible with the administration of δ-opiates, potential implications for organ preservation arise. In fact, using hibernation triggers to extend organ viability has been done successfully in many models including myocardial protection.[98] Sun et al[99] hypothesized that a δ-opioid receptor agonist (pentazocine) would decrease the severity of postresuscitation myocardial dysfunction and improve survival. In this study,[99] all animals were administered pentazocine 5 min after untreated VF and 3 min before CPR. Left ventricular rate of pressure increase at 40 mmHg and cardiac index were significantly improved with easy defibrillation, and significantly longer survival was noted. The concept of pharmacologic hibernation employing a δ-opioid receptor agonist is a novel and promising intervention for minimizing global ischemic injury during CPR and postresuscitation myocardial dysfunction.[98,99]

Free Radical Inhibitors

Free radicals release plays a considerable role in the process of postresuscitation myocardial impairment. Administration of 21-aminosteroids (lazaroids) during CPR has contributed to the improvement of postresuscitation function and better neurologically normal survival. Lazaroids exert their antilipid preoxidation action via free radical scavenging and potent cell membrane stabilization.[100] Zhang et al[25] demonstrated that by inhibiting nitric oxide production with nitric oxide synthase (NOS) inhibitor during a myocardial ischemia-reperfusion sequence, coronary sinus free radical concentration was significantly diminished and accumulation of the peroxynitration product was abolished. Various competitive inhibitors of the NOS enzyme have been shown to reduce reperfusion injury in various settings; thus, NOS inhibitors deserve further evaluation cardioprotective agents against reperfusion injury.[21–25]

Prevention of Intracellular Calcium Overload

The postfibrillatory dysfunction has been proposed to be a consequence of myocyte calcium overload that progressively occurs during VF even in the absence of ischemia. Transient myocyte calcium overload will lead to reduced calcium responsiveness of the myofilaments. Accordingly, calcium overload occurring during VF may lead to reduced calcium responsiveness of the myofilaments and thus cause postfibrillatory myocardial dysfunction. Early additional therapy targeting intracellular calcium overload may normalize myocyte Ca^{2+} and partially prevent postresuscitation stunning.[56]

Pharmacologic Defibrillation

The role of sodium-hydrogen exchanger in VF is a promising horizon. Ayoub et al[100] identified activation of the sarcolemmal sodium-hydrogen exchanger isoform-1 (NHE-1) as a potentially important pathogenic target and demonstrated, in rat models of VF and resuscitation, that NHE-1 inhibition can ameliorate myocardial abnormalities relevant to cardiac resuscitation. In these models, NHE-1 inhibition reduced ischemic contracture during VF (improving the hemodynamic efficacy of chest compression), minimized postresuscitation ventricular ectopic activity (preventing recurrent VF), and lessened postresuscitation myocardial dysfunction. Wirth et al[102] reported, in a swine model of regional coronary occlusion, similar antiarrhythmic effects of NHE-1 inhibition associated with preservation of the action potential duration. NHE-1 inhibition using the potent and selective inhibitor (cariporide) prevents stony heart and enables chest compression to maintain a coronary perfusion pressure above resuscitability thresholds.

Therapeutic Hypothermia During CPR

It is known that low body and brain temperature during cardiocirculatory arrest improves the neurologic outcome following these events. On the basis of the published evidence to date, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation made the recommendations that unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 h when the initial rhythm was VF. Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.[103] Mild hypothermia is thought to suppress many of the chemical reactions associated with reperfusion injury. These reactions include free radical production, excitatory amino acid release, and calcium shifts, which can in turn lead to mitochondrial damage and apoptosis.

Despite these potential advantages, hypothermia can also produce adverse effects, including arrhythmias, infection, and coagulopathy. Cooling should probably be initiated as soon as possible after restoration of spontaneous circulation but appears to be successful even if delayed up to 6 h.[102,103] In the European study,[104] the interval between restoration of spontaneous circulation and attainment of a core temperature of 32°C to 34°C had an interquartile range of 4 to 16 h; however, further research is needed to determine the optimal duration of therapeutic hypothermia, optimum target temperature, rates of cooling and rewarming, and the cooling techniques and monitoring.[103–105]

Community Education and Staff Training

The duration of cardiac arrest prior to the start of CPR in human victims is the best single predictor outcome; this will reflect the importance of early bystander CPR and rapid defibrillation as major contributors in the survival after cardiac arrest.[106] Therefore, it is logical to bring 4-min defibrillation into the home, where 70% of cardiac arrests occur. Public access defibrillation (PAD) is available to achieve this goal; it is inexpensive, self-instructional, easy to operate, and automatic, requiring no diagnostic ability (the AED). Survival after cardiac arrest due to VF when nonmedically qualified personnel use an AED has ranged from 0 to 54% according to the degree of community education.[7] Efforts are needed to emphasize that after 4 to 5 min of cardiac arrest without defibrillation, bystander CPR is essential and it should be performed even if a defibrillator is present, and for 2 to 3 min before defibrillation. PAD when combined with CPR in some settings outside hospitals resulted in a very large percentage of victims defibrillated within 4 min and a > 50% long-term survival rate.[108–110] Hallstrom et al[110] reported more survivors to hospital discharge in the units assigned to have volunteers trained in CPR plus the use of AEDs than those in the units assigned to have volunteers trained only in CPR. This is consistent with the concept of the large, multicenter National Heart, Lung, and Blood Institute study[111] in the United States and Canada; training was provided to lay volunteers, and AED sites had twice the number of survivors.

Conclusion

Successful CPR needs redefinition. Postresuscitation myocardial dysfunction is recognized as a leading cause of early death following initially successful CPR. It could be a true stunning phenomenon, and this phenomenon is a reversible process, so it deserves more effort and early detection to avoid its progress to stony heart. Early defibrillation is the key, provided it has been applied in the proper phase. Further studies are warranted to highlight the concept of postresuscitation disease and its hemodynamic sequences. Introducing KATP openers, δ-opioid receptor agonists, antioxidants, intracellular calcium load modifiers, a sodium-hydrogen exchanger, and therapeutic hypothermia in the era of CPR are still in the experimental stages and need further studies. However, we need to standardize the conventional methods during CPR, reinforce the concept of PAD, have a well-trained team for prompt intervention, as well as promote public education to improve the outcome after successful resuscitation. There is an urgent need to revise the guidelines for CPR in community setting, but how? It is a matter of where and when it is of enough value to be efficacious and cost-effective.

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