Review Article

Pathophysiology and hemodynamic of postresuscitation syndrome

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ABSTRACT

The fatal outcome of victims after initially successful resuscitation for cardiac arrest has been attributed both to global myocardial ischemia during the cardiac arrest and the adverse effects of reperfusion. Postresuscitation syndrome comprises 2 major components; pathophysiologic postresuscitation disease and postresuscitation hemodynamic changes. Both components predict the myocardial function, which in its turn will outline the outcome of the resuscitation effort. Awareness of those components before and early after restoration of the circulation will improve the outcomes of cardiopulmonary resuscitation.

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Postresuscitation syndrome comprises 2 major components; inflammatory (postresuscitation disease) and postresuscitation hemodynamic changes. Both components predict the myocardial function, which in its turn will outline the outcome of the resuscitation effort. Twenty to forty percent of patients who sustained cardiac arrest are initially resuscitated but only 10% survive to hospital discharge.[1,2] Successful resuscitation is not a momentary event, and the long-term outcome should be the aim. There is a marked but reversible form of systolic and diastolic myocardial dysfunction with life-threatening ventricular ectopic dysrhythmias, which compromises 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 both to global myocardial ischemia during the cardiac arrest, and the adverse effects of reperfusion.[3,4] The awareness of the pathophysiology before, during and early after restoration of the circulation is of crucial importance to improve the outcomes of cardiopulmonary resuscitation (CPR). Braunwald and Kloner[5] defined "the stunned myocardium" as a prolonged postischemic myocardial dysfunction with an eventual return of normal contractile activity. Stunning is now thought to occur in several clinical situations including delayed recovery from effort angina, unstable angina, coronary revascularization, ischemic cardioplegia, respiratory arrest, electroconvulsive therapy, cardiac transplantation, and cardiac arrest.[1-3,5-7] However, the resuscitation process seems to be more complicated and warrants understanding to explain the high variable outcomes. The cellular and hemodynamic levels during and soon after resuscitation are underestimated so far.

Hemodynamic changes after cardiac arrest. ***Post-resuscitation syndrome***. It is a status of myocardial dysfunction after the restoration of circulation by successful resuscitation that manifests by increased cardiac filling pressures, decreased cardiac index and a decrease in both systolic and diastolic function. Severe but temporary left ventricular systolic

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(LV) and diastolic dysfunction may follow 10-15 minutes of untreated cardiac arrest and successful resuscitation. However, prolonged CPR will progress to the irreversible stage of myocardial dysfunction. The dramatically global nature of this systolic dysfunction after resuscitation has been demonstrated with echocardiography, as well as ventriculography causing a decrease in ejection fraction, a decrease in fractional shortening, a decrease in dP/dt, a decrease in peak systolic left ventricular pressure/end systolic volume ratio, and a rightward shift in the pressure volume relationship. The initial lower ejection fraction (EF) post CPR is a predictor for lower cardiac index post resuscitation and the development of multiorgan failure in the next 24 hours.[2,3,8] The first study in an intact in vivo model[2] demonstrated that marked stunning of the myocardium does occur after successful resuscitation from cardiac arrest. Left ventricular pressures, cardiac index and hemodynamically measured isovolumic relaxation time all confirmed left ventricular systolic and diastolic dysfunction. Full recovery was found by 48 hours. In the second case,[6] sudden respiratory arrest occurred during a dental procedure. Echocardiogram revealed diffuse hypokinesis of LV with normal LV size and EF of 25%. After 2 weeks, multiple gated acquisition (MUGA) scan and stress echocardiogram were completely normal. According to the fact that myocardial stunning includes the persistence of left ventricular dysfunction after the return of normal myocardial blood flow, myocardial blood flow might be unchanged between baseline levels and that found at 5 hours after resuscitation, even though left ventricular ejection fraction (LVEF) remained markedly decreased by 5 hours. These data convincingly show that the phenomenon of postresuscitation myocardial dysfunction is an example of acute, but reversible heart failure and aggressive support is indicated during the first 48-72 hours. Good long-term outcome is possible if this early severe period of dysfunction can be overcome. On the contrary, prolonged and ineffective CPR will cause progressive reductions in LV diastolic and stroke volume and increases in LV free-wall thickness and stiffness resulting in the "stone heart", which is a severe and irreversible form of ischemic contracture.[9,10]

Determinants of postresuscitation myocardial stunning. ***Duration of cardiac arrest.*** The most significant factor for developing postresuscitation myocardial dysfunction is the prolonged resuscitation effort. The LVEF and pulmonary artery wedge pressure were significantly worse postresuscitation after 15 min of ventricular fibrillation (VF) compared with only 10 min of VF.[11] Progressive impairment in diastolic function terminates in a stone heart after prolonged intervals of cardiac arrest.[9] The University of Arizona Resuscitation Research Group has been investigating postresuscitation myocardial dysfunction with invasive and noninvasive measurements of LV before and after 10 and 15 minutes of untreated cardiac arrest. After 10 minutes of untreated VF, we observed the maximal dysfunction at 6 hours with partial resolution by 24 hours and full recovery by 48 hours indicating that postresuscitation myocardial dysfunction is a true stunning phenomenon. After 15 minutes of VF, no data could be obtained at 24 hours because all subjects died overnight.[11] Such data suggest that transient left ventricular failure postresuscitation can be life threatening and resuscitation should not be delayed or prolonged.[1,2,9,11] The duration of cardiac arrest prior to the start of CPR in human victims is the best single predictor of outcome.[12] Efforts are needed to educate and train the public, emphasizing that after 4-5 minutes of cardiac arrest without defibrillation, bystander CPR is essential. It should be performed, even if a defibrillator is present, for 2-3 minutes before defibrillation.[13]

Phases of cardiac arrest. Three phases have been identified during cardiac arrest; the first is the electrical phase, which lasts about 5 minutes wherein defibrillation is the priority.[14] The use of automated external defibrillators (AEDs) within 3 minutes following the onset of VF resulted in the highest ever-reported survival of 70%. Survival from VF cardiac arrest declines approximately 7-10% for each minute without defibrillation.[15] The second phase is the hemodynamic phase that lasts from 4-10 minutes; during that time circulatory support using chest compression is the priority.[16] During the hemodynamic phase, LV becomes empty as blood shifted to the right side. The third phase is the metabolic phase,[14] wherein drugs and hypothermia can be used. In the second and third phases of cardiac arrest, perfusion is critical in maintaining coronary perfusion pressure and vital to survival. The use of AED can be harmful in the last 2 phases. Electrical shock in patients with prolonged VF results in defibrillation not to a perfusing rhythm but to a pulseless electrical activity.[17] Thus, the methodology of CPR and its application according to the appropriate phase of cardiac arrest plays pivotal role in the fate of the postresuscitation myocardial function.[18]

Postresuscitation disease. The postresuscitation disease is a specific pathophysiologic state of vital organ systems early after ischemic anoxia. Adrie et

al[19] hypothesized that postresuscitation disease may be related to an early systemic inflammatory response, leading to an exacerbation of the inflammatory balance and could 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-alpha (TNF-[alpha]) and interleukin-1beta, are known to depress myocardial function. Tumor necrosis factor-alpha and interleukin-1beta synthesized and released in response to the stress of global ischemia accompanying cardiac arrest play an important role in the development of postresuscitation LV dysfunction as well.[19-21] The hemodynamic effects of TNF-[alpha] are characterized by decreased contractility, reduced ejection fraction, decreased systemic vascular resistance, hypotension, and biventricular dilation.[22,23] All of these hemodynamic changes, with the exception of a decrease in systemic vascular resistance, characterize the resuscitated myocardium.[23] The typical decreases in myocardial contractility (LV dP/dt), ventricular dilation (suggested by the decrease in cardiac output and stroke volume accompanied by no change in LV end-diastolic pressure), and hypotension were confirmed in one study.[21] In this study, systemic vascular resistance was elevated above control values during the postresuscitation observation period and is probably related to endogenous catecholamine release following resuscitation resulting in increased peripheral arterial tonus. Tumor necrosis factor-alpha is believed to exert its myocardial depressant effects by disrupting calcium homeostasis or calcium sensitivity and the normal myocardial contraction-relaxation cycle.[24]

The role of ischemia. During ischemia, there is a reduction in both creatine phosphate and adenosine triphosphate (ATP). With reperfusion; there is an 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.[25,26] Ischemia-reperfusion injury is thought to be due to the generation of oxygen-derived free radicals such as the superoxide and hydroxyl radicals. Such free radicals lead to lipid peroxidation, cellular dysfunction and stunning of myocardium. Numerous studies have implicated the nitric oxide-peroxynitrate pathway in ischemia reperfusion injury. Reperfusion and reoxygenation could play an important precipitating role in postresuscitation myocardial dysfunction.[27-29]

Chest compression. The weakest links in the chain of survival after out-of-hospital cardiac arrest due to ventricular fibrillation 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.[30] Accordingly, with a ratio of 15 compressions to 2 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 given first and followed by chest compressions.[18]

Hallstrom et al[31] have 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 the now standard CPR by compression plus ventilation. Wik et al[32] agreed that CPR first prior to defibrillation offered no advantage in improving outcomes for some cases or patients with ambulance response times shorter than 5 minutes. However, patients with ventricular fibrillation and ambulance response intervals longer than 5 minutes had better outcomes with CPR first before defibrillation were attempted. Interruptions of precordial compression for rhythm analyses that exceed 15 seconds before each shock compromise the outcome of CPR and increase the severity of postresuscitation myocardial dysfunction.[33]

Fibrillation and defibrillation. The normal balance of myocardial energy supply and demand is disrupted during VF because the demand of the myocardium for energy exceeds that 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.[34] 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.[35] Patients with ventricular fibrillation 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 increase the intracellular Calcium, a similar lesion underlies mechanical dysfunction after successful defibrillation has been reported.[36]

Electrical shocks that defibrillate hearts successfully also produce myocardial injury and this injury increase the higher energy shocks. It was thought that this injury occurs only in settings in which the myocardium is underperfused. 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.[37-39] High-energy defibrillator produces more severe LV dysfunction while fixed low energy biphasic waveform defibrillator significantly reduces the severity of postresuscitation myocardial dysfunction compared with escalating monophasic energy defibrillator.[40,41] Leng et al[42] found 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 minutes while the systolic function was much better with biphasic shocks.[41,42]

In conclusion, postresuscitation syndrome comprises 2 major components: pathophysiologic postresuscitation disease and postresuscitation hemodynamics. Both components predict the myocardial function, which in its turn will outline the outcome of the resuscitation effort. Awareness of those components before and early after restoration of the circulation will improve the outcomes of CPR.

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