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Cardiac Arrest: Resuscitation and Reperfusion

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Abstract

The modern treatment of cardiac arrest is an increasingly complex medical procedure with a rapidly changing array of therapeutic approaches designed to restore life to victims of sudden death. The two primary goals of providing artificial circulation and defibrillation to halt ventricular fibrillation continue to evolve since they were established 60 years ago. The evolution of artificial circulation includes efforts to optimize manual CPR, external mechanical CPR devices designed to augment circulation, and may soon advance further into the rapid deployment of specially designed internal emergency cardiopulmonary bypass devices. The development of defibrillation technologies has progressed from bulky internal defibrillators paddles applied directly to the heart, to manually controlled external defibrillators, to automatic external defibrillators that can now be obtained over-the- counter for widespread use in the community or home. But the modern treatment of cardiac arrest now involves more than merely providing circulation and defibrillation. As suggested by a three phase model of treatment, newer approaches targeting patients who have suffered a more prolonged cardiac arrest include treatment of the metabolic phase of cardiac arrest with therapeutic hypothermia, agents to treat or prevent reperfusion injury, new strategies specifically focused on pulseless electrical activity, which is the presenting rhythm in at least one-third of cardiac arrests, and aggressive post resuscitation care. There are discoveries at the cellular and molecular level regarding ischemia and reperfusion pathobiology that may be translated into future new therapies. On the near horizon is the combination of advanced cardiopulmonary bypass plus a “cocktail” of multiple agents targeted at restoration of normal metabolism and prevention of reperfusion injury, as this holds the promise of restoring life to many patients for whom our current therapies fail.

Keywords

Cardiac arrest; resuscitation; reperfusion

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Introduction

Sudden cardiac arrest (SCA) is an important public health challenge. Despite a dramatic decrease in the age-adjusted risk of SCD, the cumulative number of fatal SCA cases in the United States remains large. Estimates range from fewer than 170,000 fatal SCA cases per year to greater than 450,000; a figure in the range of 300,000 to 370,000 per year is likely the best current estimate.[1] SCA appears to account for approximately 50% of all cardiovascular deaths,[2] and it is estimated that 50% of the SCAs are the first clinical expression of previously undiagnosed heart disease.[2, 3] Most out-of-hospital cardiac arrests (80%) occur in private homes or other living facilities.[4] Electrical mechanisms associated with SCA are broadly classified into tachyarrhythmic and non-tachyarrhythmic categories, the latter including pulseless electrical activity (PEA, formerly referred to as electromechanical dissociation [EMD]), asystole, extreme bradycardia and other mechanisms, often associated with non- cardiac factors. This article aims to review the cardiac rhythms associated with sudden death, the pathophysiology involved in cardiac resuscitation, and the current state of resuscitation science and techniques.

Ventricular Fibrillation

In 2002, Weisfeldt proposed a “three-phase” time dependent model for treatment of cardiac arrest from ventricular fibrillation and pulseless ventricular tachycardia that remains at the forefront of our current treatment paradigm.[5] The first or electrical phase of cardiac arrest lasts for about 5 minutes and is characterized by the need for rapid defibrillation as the top priority. Indeed survival rates for out of hospital cardiac arrest can exceed 60% for patients within this early electrical phase. The second phase or circulatory phase of cardiac arrest last from about 5 minutes to 10 minutes following initiation of ventricular fibrillation. It appears during this circulatory phase that the best therapy is to first give a brief period of vigorous chest compressions (between 100 and 300, the exact duration is not really known), followed by defibrillation. This implies that during this phase the immediate treatment of VF is not traditional defibrillation first rather chest compression first. The concept is that the initial vigorous chest compressions provide blood flow to the myocardium that improve the chances of successful defibrillation and long term survival. This concept is not currently incorporated within the American Heart Association guidelines in part because it is not possible to know exactly which phase a person is in and it would make the teaching of ACLS even more complicated. Weisfeldt also speculated on the existence of a third or metabolic phase of cardiac arrest that begins about 10 minutes after the arrest. The treatment of patients who have remained without circulation for a very prolonged cardiac arrest interval is difficult and in practice most deaths from cardiac arrest are from within this phase. During this metabolic phase the model suggests that both compression and defibrillation are no longer sufficient therapies to routinely save lives of cardiac arrest victims. Metabolic resuscitation of some form is optimally required. It is during this phase that salvage therapies such as cardiopulmonary bypass plus metabolic drug combinations are required with components directed toward prevention and correction of reperfusion injury. A more detailed discussion of this metabolic phase and reperfusion injury is included in the second half of this paper.

Automatic External Defibrillators (AEDs)

The development of AEDs has revolutionized out-of- hospital resuscitation. AEDs monitor the ECG via self-adhesive electrodes applied to the patient's chest. Rhythm is analyzed by a microprocessor in the defibrillator and if it's algorithm detects ventricular fibrillation, devices either sound an alarm that a shock is advised, or in completely automatic versions, a defibrillation shock is delivered after an audible warning to stand clear. Specificity rates of the ventricular fibrillation detection algorithm approach 100%. Emergency service personnel equipped with AEDs achieve higher resuscitation and survival rates than those equipped with manual defibrillators or no defibrillators at all. This is likely due to the reduced time to first-shock delivery with AEDs. Widespread AED availability in the community has proven to be beneficial in improving survival from prehospital cardiac arrest. In a large public-access defibrillation study, there were significantly more survivors to hospital discharge in scenarios where lay volunteers were trained in AED use and CPR (23%) as opposed to CPR alone (14%).[6] Similar benefit has been demonstrated for AEDs used in schools as well as by police.[7, 8] However public access AEDs are involved in only a modest fraction of all cardiac arrests and widespread early use remains a challenge.

Chest Compression

When defibrillation fails to restore circulation, restoration of blood flow is needed.[9-11] Some measure of blood flow is generally produced by chest compression,[12] although more advanced strategies are being studied.[13] The standard is manual chest compression where the sternum is depressed at least 2 inches at least 100 times per minute, with half of the time in compression.[14] Since these manual chest compressions can be difficult to do and can cause substantial operator fatigue, mechanical devices are being studied as a way of producing more consistent chest compressions. Current mechanical devices include the LUCAS system[15] and the Load Distributing Band (Autopulse) system.[16] The LUCAS system evolved from studies of chest compression with active compressions and decompressions,[17] while the Load Distributing Band system evolved from studies of circumferential compressions with a pneumatic cuff.[18] Both devices are associated with outcomes that are similar to those obtained with manual chest compressions.[15, 16, 19] In addition, the combination of a manual system that provides active compressions and decompressions, as well as the impedance threshold device,[20] which impedes the flow of air out of the chest during chest decompression, was shown to be associated with outcomes that were improved over those obtained with standard chest compressions.[21] In a large randomized trial of conventional manual CPR, however, the impedance threshold device compared to sham did not improve survival.[22] Finally, the amount of ventilation that is required for successful resuscitation remains to be clarified.

Pulseless Electrical Activity (Pea)

At present, there is no single unifying definition for PEA. Moreover, in contrast to the proven therapy of early defibrillation for ventricular fibrillation, less is known about effective therapies for PEA. The common denominator is the presence of spontaneous organized cardiac electrical activity, in the absence of blood flow sufficient to maintain consciousness, and the absence of rapid spontaneous return of circulation.[23] The latter qualifier excludes transient losses of blood flow, such as vaso-vagal syncope, that have clinical implications different from true PEA. PEA is thus defined as a syndrome characterized by absence of a palpable pulse in an unconscious patient with organized electrical activity other than ventricular tachyarrhythmia on ECG.

PEA can be classified into three groups/stages:normotensive PEA, pseudo-PEA, and true PEA. Normotensive PEA occurs in the situation of baseline cardiac contractions and myocardial fiber shortening and typically occurs secondary to an extra-cardiac problem, such as tension pneumothroax or tamponade. Pseudo-PEA is defined as the situation with weak myocardial contractions that only produce detectable aortic pressures as measured by invasive monitoring or echocardiography.[24] True PEA is total absence of myocardial contractions, which is typically the final stage of PEA that occurs after prolonged exposure to acidosis/hypoxia/increased vagal tone.[24]

The overall Resuscitation Outcomes Consortium (ROC) survival rate for treated patients with PEA arrests surviving to hospital discharge was approximately 8%. This compares with 30.5% for VT/VF arrests. Survival from PEA arrests in public settings was 14.9% and home arrests 7.5%. Similarly low survival rates were reported by the CARES Network.[25] In a study of greater than 50,000 in-hospital cardiac arrests from the period between 1999 and 2005, the first documented pulseless rhythm was ventricular tachycardia (VT) in 3810 (7%), ventricular fibrillation (VF) in 8718 (17%), pulseless electrical activity (PEA) in 19,262 (37%) and asystole 20,129 (39%) (18). In that study, survival to hospital discharge rate was not different between those with first documented VF and VT (37% each), but was much lower in PEA and asystole (12% and 11%).

Older age is more likely to be a determinant of PEA and asystole as opposed to VF or VT,[26-28] and the proportion of PEA among cases of sudden cardiac arrest increases with age; from 10-12%in the 13-49 years age group to 18% >50 years.[29] Sex is also a significant determinant of the presenting arrhythmia during SCA, where many studies have shown that women are significantly more likely than men to manifest PEA.[26, 30] Several studies report an association between African American race and propensity to present with PEA.[26, 31, 32]

In a retrospective analysis from the Oregon SUDS, a lifetime clinical history of syncope was identified as a novel association with PEA,[26] and remained a significant determinant of PEA after adjusting for other conditions [OR 2.64 (1.31-5.32)]. The preponderance of syncope among PEA cases was not explained by an increased prevalence of conduction system disease, leading to the interesting possibility that in a sub-group of patients, severe hypotension due to peripheral vascular failure or a malignant form of vaso-vagal syncope may account for manifestation with PEA.

Mechanisms and Pathophysiology of Pea

Defining the pathobiology and management of PEA has been limited by the lack of clinically relevant laboratory models. Asphyxia is the traditional experimental method of inducing PEA arrest and this model, in varying forms, has been used since the 1960's.[33] However, asphyxia is not a common clinical cause of out-of-hospital PEA arrest in the adult population. In autopsy studies, about 50%of cases of PEA may be ascribed to a primary cardiac event.[34] In one study, PEA as the initial rhythm was observed in 50-60% of cardiac arrests with onsets witnessed by advanced rescuers (paramedics) and was not preceded by a reported respiratory event.[35] Finally, up to one-third of patients resuscitated from cardiac arrest due to PEA undergo a percutaneous intervention for acute coronary occlusion and ST-segment elevation myocardial infarction (STEMI), suggesting that PEA may be an initial arrhythmic event resulting from acute ischemia.[36]

In the 1980's PEA following countershock of prolonged, untreated VF, was introduced as a PEA model.[37, 38] This model does not replicate primary PEA; it is more similar to PEA following a shock terminating prolonged VF. Observations during resuscitation following post-shock PEA have demonstrated evidence of metabolic and electrolyte disturbances that could sustain PEA after defibrillation.[39] Whether these are causes, conditioning influences, and/or therapeutic targets requires further clarification. A possible role of the parasympathetic nervous system in primary PEA has been indirectly evaluated in an asphyxia model in which surgical or chemical (high dose atropine) vagotomy was performed after induction of PEA with asphyxia. ROSC was more likely after surgical vagotomy but high dose atropine had no beneficial effect. The mechanistic benefit of vagotomy was unclear.[40]

Cellular Mechanisms and Contractile Dysfunction

For some time, acute coronary occlusion has been known to result in a sudden loss of contractile force. The most likely cause is abrupt loss of tissue turgor, also known as the “reverse garden hose effect”.[41] The mechanism underlying the garden hose effect is uncertain, but may be related to loss of optimum cross-bridge overlap (e.g., starling forces) when the erectile effect of the vasculature is abrogated. Since intracellular calcium (Ca^{++}) is critical for regulating myocardial contraction,[42] an alternate hypothesis is that loss of vascular pressure alters vasotropic feedback that modulates triggered Ca entry or myofilament Ca sensitivity. Metabolic consequences of ischemia likely contribute to further contractile dysfunction.[43] This may be of particular importance for PEA following countershock after prolonged VF. It is important to recognize that many of the metabolic changes seen are associated with chronic heart failure as well.[44, 45] Thus, metabolic stress could also contribute to loss of contractility leading to PEA in patients with advanced heart failure.

Inotropic agents, particularly beta agonists, have been the mainstay of therapy for PEA,[46] based on considerations of molecular factors involved in contractile function and dysfunction. Beta-agonists phosphorylate L-type Ca^{++} channels (LCCs), ryanodine receptors (RyRs), the sarcoplasmic reticulum Ca-ATPase (SERCA) regulator phospholamban, and myofilaments to not only increase triggered calcium entry into the cell, but also to synchronize calcium release from a loaded SR, and improve myofilament Ca-responsiveness. There is, however, a time-dependent loss of contractile function in response to the metabolic stress of acute ischemia. Since the mechanisms for this loss are unknown, further studies to elucidate these mechanisms are needed to provide a rational basis for future therapies. In addition, whether myofilament Ca-sensitizers such as levosimendan, or other agents, may be of additional or greater benefit in the setting of PEA has yet to be determined.

Clinical associations between the presence of inflammatory cytokines and SCD have been established. In the MERLIN-TIMI 36 trial, elevation of cytokines, such as osteoprogerin, was the best predictor of early sudden death following myocardial infarction.[47, 48] Furthermore, the proposed benefit of N-3 fatty acids on cardiac mortality post MI and in heart failure settings have also been attributed at least partially to the anti-inflammatory effects of N-3 fatty acids anti-inflammatory effects.[49]

The effect of production of cytokines/cardiokines, such as tumor necrosis factor and the interleukin family of cytokines, may acutely depress cardiac function. This has been attributed to the effect on phosphatidylinositol 3 (PI3) kinase isoforms as well as lipid signaling intermediates, such as sphingosine-1, which may directly interfere with Ca signaling.[50] More recently, there has also been data to suggest that high mobility group box 1 or alarmin family of signals may also directly depress cardiac function and Ca kinetics.[51] However, this effect may be partially ameliorated through PI3 kinase gamma blockade, suggesting possible avenues for host protection.

While there has been a significant interest in the role of relaxin, a naturally occurring hormone that increase in women during pregnancy, in acute heart failure, its mechanisms of action are not well known.[52] In an animal model of acute ischemic arrest, relaxin was able to significantly reduce the adverse outcomes of asystole, ventricular tachyarrhythmias or bradycardiac arrests, possibly through anti-inflammatory effects by inhibiting mast cell activation.[53]

Further research is needed to weigh the role of immune modulation in the PEA pathway, especially in the context of underlying co-morbidities such as diabetes, heart failure and other pro-inflammatory disease states. An intriguing hypothesis, based on the possibility that beta-blockers protect against the expression of VT/VF during ischemia, is that inflammatory signals may allow PEA to emerge by default.

Changing Patterns of Sudden Cardiac Arrest

Thirty years ago, nearly 70% of the initial electrocardiograms recorded during cardiac arrests showed ventricular fibrillation or pulseless ventricular tachycardia.[23] Recent data from several large population cohorts, covering over 40,000 patients, demonstrate proportions of initial VT/VF in the range of 20-25%.[54, 55]

In a study from Seattle, all out-of-hospital cardiac arrests were studied in the years from 1979-2000. The incidence of ventricular fibrillation as the first documented rhythm changed over the twenty year study period from 61% of cardiac arrests to 41% of cardiac arrests. The incidence of asystole as the first recorded rhythm went from 21% to 31% during that same time period and for PEA, the change was from 17%to 28%.[56]

This striking decline in the frequency of VT/VF, and the relative and possibly absolute increase in PEA and asystole as the initial rhythm, may be due to a number of interacting environmental, clinical, pharmacological, or strategic interventional factors. At least one of these may be analyzed in the context of the location of cardiac arrests. From ROC data based upon 12,930 total arrests stratified by location, VT/VF occurred in 22% of 9,564 arrests occurring in homes, 13%of 1324 occurring in nursing homes or residence facilities, and 51%of 2,042 arrests occurring in a public location.[31] Thus, one might conclude that for arrests occurring in public locations and likely benefiting from rapid recognition and management, the incidence of VT/VF is not much lower than thirty years ago. However, patients who have cardiac arrests in the home, or in the nursing home, where the incidence of VT/VF is reduced, may be older, have more severe chronic conditions, or may be subject to delays in recognition and initial responses. The decline in VT/VF may also be contributed to by the increase in implantable cardioverter defibrillators (ICDs) in patients with systolic heart failure[57] and the increasing use of aggressive pharmacologic management of heart failure, particularly beta blockers,[58] which may suppress VT/VF and result in an increase in cardiac arrest related to both PEA and asystole.[59] However, these potential determinants of the increasing burden of PEA need further investigation.

Ischemia and Reperfusion/Reperfusion Injury

The biological processes that determine whether a heart will return to normal following an episode of ischemia versus fail to recover remain unknown. Of primary interest to the clinician is the controversial notion of reperfusion injury that occurs during the “metabolic phase” of cardiac arrest with prolonged cardiac arrest [28]. Reperfusion injury denotes a potentially avoidable pathological process wherein potentially viable cells die not entirely due to the cellular derangements of ischemia. [60-62] Death occurs during the reperfusion phase due to the combination of the ischemia-induced metabolic alterations plus the conditions of reperfusion specific to the sudden reintroduction of normal levels of oxygen and other substrates. Underlying the concept of reperfusion injury were studies from the 70s and 80s that observed three “paradoxes” in cells and in organs.[63]

The initial observation of a “calcium paradox” followed the observation that if normal levels of calcium were rapidly reintroduced to cardiac cells which are routinely grown in calcium free media, the cells would rapidly die upon re-exposure to the previously normal levels of calcium.[64-65] Similar studies demonstrated cell death after normalization of pH after cells were adapted to low pH conditions, as well as accelerated cell death upon reoxygenation (usually with room air 150 torr oxygen) of cells adapted to lowered oxygen levels. [66] It is now well accepted that cells grown in culture demonstrate the ability to die suddenly under the identical conditions that they once thrived in, if those baseline conditions are suddenly reintroduce after a period of metabolic deprivation or ischemia. But whether or not these cellular mechanisms are relevant for people who are undergoing emergency reperfusion treatments for regional ischemia from a coronary occlusion, or whether reperfusion injury makes any difference for those people who are having emergency resuscitation from global ischemia from cardiac arrest remains quite poorly understood and controversial. [61,63,67]

Reperfusion injury appears to be critically time dependent

Similar to the time dependency of the metabolic phase described by Weisfeldt's three phase model, there is an important time dependency for reperfusion injury. It is clear that shorter periods of ischemia do not have any reperfusion injury at all. Indeed the opposite is seen, as short intervals of complete ischemia can produce ischemic preconditioning, a state of protection and decreased injury [61,68,69]. As opposed to preconditioning protection, the concept of reperfusion injury is that after some more prolonged ischemic period the cells cross a threshold of metabolic derangement. Only after this threshold is passed will cells demonstrate reperfusion injury. This implies that before this critical threshold time is reached, immediate reperfusion is the best treatment approach to shorter periods of ischemia.[70] However, after some lengthening interval of prolonged ischemia there comes a time point at which the immediate reperfusion of normal oxygenated blood into the ischemic organ produces additional injury and death than some alternative approach for “controlled reperfusion” such as use of an anti-reperfusion injury cocktail or cooling [71-75]. While still controversial, there is much data from cellular models, animal models and even limited human studies, that this notion of reperfusion injury impacts humans under conditions of ischemia; and is relevant to clinicians under some situations of ischemic injury [76-79].

Mechanisms of reperfusion injury in the metabolic phase of prolonged cardiac arrest

The alterations during ischemia lay the foundation for subsequent reperfusion injury.[67,76] With ischemia and diminished availability of oxygen, there is a rapid reduction of ATP production and ATP levels. Without oxygen to be used as a terminal electron acceptor within the mitochondria, there is a rapid intracellular REDOX shift toward reduction (more electrons) within the cell due to a buildup of the normal electron-rich metabolites that lack the normal pathway via mitochondrial cytochrome oxidase that allows for the flow of electrons to oxygen.[80] Without oxygen for cytochrome oxidase (complex IV), this increasingly reduced mitochondrial compartment will begin to “leak” electrons directly to molecular oxygen which although reduced in level (due to ischemia) is still present in sufficient quantities for this radical generating reaction. This leak of electrons produces an elevation in superoxide and other reactive oxygen species (ROS) during ischemia[81]. At the same time lowered levels of ATP reduce the ability of the cell membranes to control ionic gradients, particularly important for Ca, K, and Na.[82] There are dramatic shifts in calcium concentration into the typically low-calcium cytosolic compartment because the ability to sequester calcium into the mitochondria matrix and endoplasmic reticulum is reduced. Loss of osmotic control and cell swelling occur as the ionic gradients are lost.

As ischemia continues, there are increasing derangements of the intermediates of central metabolisms are described in a recent metabolomics survey of the rodent heart after 30 minutes of cardiac arrest[83]. Significant increases occur in short-chain acyl carnitines (valerylcarnitine, hydroxybutyrylcarnitine, 2-methylbutyrylcarnitine, and propionylcarnitine) and 3-hydroxybutyryl CoA. These findings suggest that accumulation of branched-chain amino acids represent incomplete mitochondrial oxidation products. The accumulation of the CoAs and carnitines are likely due to the lack of oxygen to support operation of the mitochondrial oxidative phosphorylation. In addition, the organic osmolytes such as mannitol, ribitol, and sorbitol were seen to be increased, likely this is the response to the hyperosmolarity caused by the increased concentrations of inorganic ions. As expected with ischemia, carbohydrate metabolites were substantially decreased in the heart tissue, particularly metabolites in the glycolysis pathway (glucose, glucose-6-phosphate, and fructose-6-phosphate), the pentose phosphate pathway (sedoheptulose 7-phosphate), and their precursors (mannose-6-phosphate and glucose-1-phosphate). Maltotriose, maltotetraose, maltopentaose, and maltohexaose (oligomeric forms of glucose) were also substantially decreased as the heart continues to consume and deplete carbohydrates for energy generation during ischemia.

It is into this milieu of the deranged metabolism that resuscitation with reperfusion and reoxygenation brings in a sudden surge of oxygen and new substrates. A sudden and very large burst of ROS can be detected within the heart (and other organs) upon reoxygenation[84,85]. While it is generally acknowledged that this oxidative stress is a major factor in the etiology of reperfusion injury, considerable debate centers around which sources of ROS are most important and what are the primary cellular and organ targets for oxidative damage. Possible sources of ROS generation include the cytosolic NADPH-linked NOX enzymes, the inflammatory process, xanthine oxidase, and mitochondrial dysfunction[86-87]. Cellular targets include nuclear DNA (nDNA) damage, cytosolic proteins, and mitochondrial oxidative phosphorylation (OXPHOS) and mitochondrial DNA (mtDNA). An amplifying cascade of oxidative damage is set into motion wherein ROS produces damage, which then produces more ROS. Major contenders for the organs most sensitive to reperfusion include the heart and brain.

Mitochondria appear at the heart of reperfusion injury

Mitochondria act as a nexus for reperfusion injury pathways.[69,76,80,87-89] The mitochondrial are one of the most important sources of ROS within individual cells and mitochondrial OXPHOS and the tricarboxylic acid cycle enzymes are acutely sensitive to ROS damage. Therefore, the mitochondria may be important in both the generation of ROS and as a target for the functional disruption of the cell by reperfusion injury stimulated ROS[90]. If true, one would predict that the outcome of reperfusion following cardiac arrest should be made worse if either the endogenous rate of mitochondrial ROS were increased or if the mitochondrial antioxidant defenses were impaired. There is much laboratory evidence to support both of these pathways as important during reperfusion. Consistent with this is the observation that the brain and the heart are the organs most reliant on mitochondrial bioenergetics.

Calcium control mechanisms

In addition alterations due to dysfunctional calcium control also amplify the injury the injuries of ischemia and reperfusion[82]. Elevations of cytosolic calcium occur rapidly as the high concentrations of sequestered calcium in the mitochondrial and endoplasmic reticulum begin to equilibrate due to the loss of energy to maintain the gradient as well as alterations in membrane channels and receptors. Not only does this begin to uncouple mitochondrial ATP generation, but widespread activation occurs of enzymes such as calpains and other proteases, nitric oxide synthase, calcineurin, and endonucleases that produce proteolysis and widespread injury by additional pathways[91-92].

Advanced resuscitation strategies: Combining emergency cardiopulmonary bypass plus metabolic cocktails targeted toward preventing reperfusion injury

Putting the basic science of reperfusion injury biology together with the need for better circulation of blood suggests a future direction for the treatment of the metabolic phase or intractable cardiac arrest. These new approaches are likely to work well in synergy with our proven therapies such as early CPR, defibrillation, and PCI. To treat the complex metabolic dysfunction and high lethality of prolonged cardiac arrest, most experts are predicting an expansion of the use of invasive cardiopulmonary bypass in concert with drugs (very likely several drugs combined together as a “cocktail”). The use of emergency cardiopulmonary bypass (ECPR) with the ability to produce nearly normal levels of blood flow is a logical extension of CPR, but has only recently been shown to be practical for selected patients in emergency situations[93-97]. ECPR requires the placement of large cannula in a major artery and a major vein (typically femoral artery and vein). The life-saving effect of this approach has been reported primarily from Japan, where Nagao and Sakamoto and other colleagues have developed a growing network for the rapid deployment of ECPB in the emergency department[94,95]. Now available to cardiac arrest victims in over 30 cardiac arrest centers across Japan, these emergency facilities have developed the art of rapid emergency canulation, full circulatory support, and rapid PCI. They achieve full arterial and venous canulations and blood flow typically within 15 minutes after the arrival of an arrested patient[98]. The survival rates are likewise impressive given that all these patients are unresponsive to prehospital ACLS and emergency department ACLS efforts for at least 10 minutes. While the survival rate of these patients would be predicted to be less that 1% in most US emergency departments, the Japanese experience would suggest that survival rates with good neurological function of greater than 15% are possible in these selected patients[95,98]. Another advantage of using full circulatory support, is that it also allows for very rapid PCI treatment of an occluded coronary artery. Rapid PCI is a vital component of the use of ECPB to prevent myocardial necrosis and the long term sequela of coronary occlusion. It is possible that the most significant value of ECPR will be when it is coupled with a metabolic strategy against reperfusion injury (i.e. an anti-reperfusion injury cocktail). The clearest demonstration of this potential value comes from the experimental laboratory of Buckberg and colleagues who reported results of swine experiments with a lethal period of brain ischemia[71,72,74,99-101]. They subjected swine to 30 minutes of complete brain ischemia, a time period that is universally devastating. The experimental group received an anti-reperfusion injury cocktail that included hypocalcaemia, hypomagnesaemia, alkalosis, hyperosmolarity and blood conditioned via a white blood cell filter. This cocktail was circulated around within the vessels of the brain for 20 minutes prior to reestablishment of recirculation of normal blood[100]. The control group received normal blood reperfusion as would be the practice now. All of the control animals as expected died with extensive brain injuries. However the experimental group all survived (6/6), with good neurological function in the majority of animals. This study is a dramatic demonstration of the potential of the ECPB plus cocktail approach. Yannopoulos and colleagues have taken a similar approach and are likewise now able to routinely resuscitate swine from 15 and 20 minutes periods of cardiac arrest, a resuscitation feat almost never before reported in the literature[102,103]. They are using a bundle of techniques including manual CPR techniques to maximize blood flow including vigorous chest compression, abdominal binding, drugs targeted to mitochondria and membrane integrity, and using the inspiratory threshold device[102,103]. These advanced CPR techniques produce much higher blood flow than standard CPR. But improving blood flow alone is not sufficient to produce survival from these longer periods of cardiac arrest. They have worked with cocktails that include NO, isoflurane, polaxymar 188 [102,103]. What they report from these studies supports the notion that the combination of improved blood flow along with metabolic therapies will produce survival from what was a previously uniformly fatal period of cardiac arrest. It is possible that the future of resuscitation will involve this approach, as it is the most currently viable method for treatment of the patients in the metabolic phase of cardiac arrest.

Collectively these data tell us that while early cardiac arrest can be treated successfully with current therapies, new therapies will be required to surmount the metabolic phase of cardiac arrest. However the data also increasingly suggest that this metabolic phase need not be universally fatal. With new research initiatives and research funding, markedly improved survival rates could become the norm within a decade. The best hope to achieve this vision is to couple current proven therapies such as early defibrillation and early CPR with evolving strategies derived from investigations such as the rapid deployment of ECPR and PCI in conjunction with a metabolic strategy targeted at avoiding reperfusion injury, restoring normal mitochondrial function, and returning tissues to metabolic homeostasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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