Outcomes after cardiac arrest remain poor more than a half a century after closed chest cardiopulmonary resuscitation (CPR) was first described. This review article is focused on recent insights into the physiology of blood flow to the heart and brain during CPR. Over the past 20 years, a greater understanding of heart–brain–lung interactions has resulted in novel resuscitation methods and technologies that significantly improve outcomes from cardiac arrest. This article highlights the importance of attention to CPR quality, recent approaches to regulate intrathoracic pressure to improve cerebral and systemic perfusion, and ongoing research related to the ways to mitigate reperfusion injury during CPR. Taken together, these new approaches in adult and pediatric patients provide an innovative, physiologically based road map to increase survival and quality of life after cardiac arrest. (Anesth Analg 2015;XXX:00–00)

Sudden cardiac arrest remains a leading cause of prehospital and in-hospital death. Efforts to resuscitate patients after cardiac arrest have preoccupied scientists and clinicians for decades. However, the majority of patients are never successfully resuscitated. Based on the published reports, the overall survival rates after cardiac arrest are grim, ranging from 1% to <20% for out-of-hospital nontraumatic cardiac arrest and <40% for in-hospital cardiac arrest. Of these, 10% to 50% have poor neurological function. Surprisingly, the physiologic principles that underlie the life-saving process of cardiopulmonary resuscitation (CPR) remain only partially understood and are often controversial. Some would argue that current approaches to cardiac arrest are fatally flawed, and that is why the overall survival rates have hovered around 7% for out-of-hospital cardiac arrest and <30% for in-hospital cardiac arrest nationwide for a half a century. This review article is primarily focused on recent advances in the field of CPR, with primary focus on new ways to promote better perfusion to the heart and brain. There have been significant advances in our understanding of the physiology of resuscitation over the past 2 decades, with new insights into the physiologic mechanisms that regulate blood flow to the vital organs, common errors in the delivery of CPR that often reduce its effectiveness, ways to enhance circulation into the physiologic mechanisms that regulate blood flow to the heart and brain during CPR, and new approaches to reduce injury associated with reperfusion. Given the debate surrounding what is known, what we think we know, and what remains unknown about resuscitation science, this article also provides some contrarian and nihilistic points of view.

When the cause of the arrest is reversible, the primary treatment goal of sudden cardiac arrest is to fully restore cardiac and brain function. The leading causes of cardiac arrest, such as a primary or ischemia-induced arrhythmia, pulmonary emboli, hemorrhage, trauma, or medication/drug overdose, all require emergent efforts to increase cardio cerebrovascular circulation. The critical first step to successful resuscitation is restoring blood flow with sufficient aortic pressure. Understanding the complex physiology of cerebrovascular perfusion during CPR is crucial to reducing morbidity and mortality after cardiac arrest. Vital organ flow enhancement is critical, but often by itself insufficient, to fully restore life after cardiac arrest.

There are multiple areas in resuscitation science where significant knowledge gaps and unmet needs limit our ability to consistently restore full life after cardiac arrest. First is the need for greater blood flow than the minimal amount produced by conventional closed chest cardiac massage, the most commonly used method of CPR that has not changed for over a half a century. Second is the need for tools that help provide better quality CPR. Third is the need to reduce the potential for brain injury associated with the simultaneous arterial and venous pressure compression waves focused toward the brain each time the chest is compressed. Fourth is to prevent reperfusion injury in the first seconds and minutes of reperfusion, especially after prolonged periods of no flow. The fifth large area where there are unmet clinical needs is in postresuscitation care, which is beyond the scope of this review.

In what follows, we try to highlight some recent advances in resuscitation science aimed at addressing these unmet needs and to discuss why some with doubts believe that there is a lack of progress. We leave it to the reader to decide whether progress is being made, whether we are simply treading water, or whether the science of resuscitation is actually regressing.

CONVENTIONAL CPR PHYSIOLOGY

The Compression Phase

Conventional or standard (S)-CPR is performed with a pair of hands. With each chest compression, intrathoracic...
pressure is increased, and the heart is squeezed between the sternum and the spine. With each compression, both the aortic and the right atrial pressures increase, with right atrial pressure similar to, or sometimes higher than, left-sided pressures. Blood is propelled forward from the nonbeating heart toward the brain, coronary arteries, and the rest of the body because of the presence of the 1-way valves within the heart and pressure differences between the thorax and the nonthoracic regions. Within the past decade, there has been renewed interest in the effect of increased intrathoracic pressure on intracranial pressure (ICP) during the compression phase. During this phase, ICP is increased, which in turn increases resistance to cerebral perfusion. It is speculated that the increase and decrease of ICP during CPR is secondary to changes in intrathoracic pressure transduced through the paravertebral venous/epidural plexus and spinal fluid to the intracranial compartment. ICP increases with each positive pressure ventilation. The increase in ICP and the simultaneous decrease in the calculated cerebral perfusion pressure (CerPP) are shown in Figure 1 (0° supine tracings). Right atrial, right ventricular, and pulmonary artery pressures increase in parallel with each compression. During CPR, the coronary artery perfusion pressure is generally calculated as the difference between the aortic and the right-sided pressures. Thus, high right-sided pressures during S-CPR also limit coronary perfusion pressures. The authors speculate that one of the reasons patient outcomes with some methods of CPR, including S-CPR, are so poor is that not enough attention is focused on understanding the interactions among the changes in right-side cardiac pressures, ICP, and the resultant cerebral and coronary perfusion pressures.

Common Errors During Chest Compression

Preclinical and clinical studies support the American Heart Association (AHA) recommendation that chest compressions should be 5-cm deep. When the chest is compressed too slowly, too rapidly, too much, or too little, clinical outcomes are adversely affected. Interruptions in chest compressions are harmful. Obviously, without chest compressions, there is no forward blood flow. Too often, rescue personnel stop chest compressions for over a minute to intubate, feel for pulses, auscultate the chest, and/or check the underlying rhythm. In the heat of the moment, rescuers often forget to perform high-quality CPR. These common errors significantly and adversely affect outcomes.

A recent analysis of CPR quality during a large National Institutes of Health Resuscitation Outcomes Consortium Prehospital Resuscitation using an Impedance valve and Early versus Delayed (ROC PRIMED) trial demonstrated that these errors were common and harmful. Nearly half of the time, compressions were performed at rates and depths outside of the recommended range of the AHA guidelines. At least one-third of the subjects had compression rates in excess of 120 per minute, and survival rates were poorer at these higher rates. We speculate that at higher rates of compression, diastolic filling times may be too short, and compression depth and full recoil may not be achieved. Most importantly, lack of compliance with study performance protocols and AHA guidelines in this trial was associated with worse outcomes (Fig. 2).

*Additional analyses of the ROC PRIMED study for this review (reference 30) were performed by Drs. Yannopoulos and Duval.*
Cardiopulmonary Resuscitation Review

The Chest Decompression Phase

The physiology of the decompression, or chest recoil, phase of CPR is complex. Its importance during CPR has been only recently better understood. During the decompression phase, the heart is refilled after it has emptied from the previous chest compression. This refilling process is extremely inefficient during CPR, especially during S-CPR when passive chest wall recoil provides the only force able to draw blood back into the right side of the heart. This effect may be even more accentuated in individuals in whom chest recoil is impaired, including patients with broken ribs. In addition to enhancing venous return to the heart, ICP is reduced during the decompression phase. Each time the chest wall recoils, ICP decreases based on the same pressure transference mechanisms that increase ICP during the compression phase. This is shown in Figure 1 (0° supine tracings). These changes in ICP during the compression and decompression phases help to determine the level of cerebral perfusion during CPR.

Common Errors During Chest Decompression

The slight vacuum generated inside the thorax during passive chest recoil draws some blood back into the heart and some air into the lungs. This in turn draws blood from the extrathoracic to the intrathoracic space and partially refills the heart before the next compression. If rescue personnel inadvertently lean on the chest, preventing it from fully recoiling after each compression, then intrathoracic pressure remains greater than atmospheric pressure. This common error reduces the refilling of the heart and the reduction in ICP that occurs with full chest wall recoil. Studies in animals have shown that incomplete chest recoil, or leaning on the chest after the chest compression motion is complete, markedly reduces perfusion pressures to the brain and myocardium. Similarly, compressing and decompressing the chest too rapidly (>120/minute) reduces the venous return time below what is needed to refill the heart. These errors in technique adversely affect survival rates.

Positive Pressure Ventilation During CPR

During CPR, each positive pressure breath inflates the lungs, facilitates O₂ delivery, and opens up the pulmonary arterial and venous vasculature, allowing for respiration and transpulmonary circulation. Each of these functions is critical. As well described by West, too little positive pressure (low rates and/or tidal volume) will not provide adequate blood oxygenation and too much (excessive rates and/or tidal volumes) may increase pulmonary vascular resistance. The interactions among the heart, lungs, and brain during positive pressure ventilation (PPV) are complex. A positive pressure breath increases intrathoracic pressure, which reduces venous return to the right side of the heart. The increase in intrathoracic pressure also momentarily increases right ventricular afterload. The end result is a decrease in right ventricular preload and an apparent increase in afterload. At the same time, the positive pressure breath increases the volume of West Zone I and decreases the volume of West Zone III, which effectively “squeezes” pulmonary venous blood into the left side of the heart. Thus, each positive pressure breath results in a temporary increase in left ventricular stroke volume through the Starling mechanism during normal cardiac function.

In addition, PPV affects ICP and CerPP. Each positive pressure breath instantly increases ICP, thus generating increased resistance to forward brain flow. A second and less understood impact of PPV is the effect on CO₂ exchange. Etco₂ values during CPR are believed to reflect circulation. Hypoventilation results in decreased CO₂ clearance. Studies in animals suggest that high Paco₂ levels during CPR are detrimental. In the absence of autoregulation, less is known about the role of Pco₂ in regulating cerebral perfusion during CPR.

The net effect of these changes during CPR after cardiac arrest is less well characterized; however, the balance between circulation and respiration during CPR is obviously critical. There may not be a one-size-fits-all ventilation strategy for all patients or for the many different methods of CPR. Unfortunately, it is difficult to obtain prospective clinical data related to this issue in the setting of cardiac arrest.

Over the past 20 years, PPV, essential for providing O₂ and removing CO₂, has proven to be important, but not as essential as chest compression, during CPR. Some have promoted the performance of chest compressions only, with no ventilations, for the first several minutes of CPR. Compressions only, rather than compressions and mouth-to-mouth rescue breathing, are easier for a 911-dispatcher to teach and a lay rescuer to effectively perform. However, there are no prospective...
randomized studies in support of the chest compression-only approach, which was, in part, a backlash to the excessive ventilation rates observed clinically.6 As described further below, excessive ventilation rates were found to be harmful in animals.6 Based on the animal data and a consensus of experts, the AHA recommends a compression:ventilation ratio of 30:2 for basic life support and continuous chest compressions at a rate of 100 with asynchronous ventilations every 10 compressions for advanced life support.105,106 The ventilation tidal volume should be approximately 600 mL, which, for most adults, is approximately 8 mL/kg, so as to minimize CPR-induced ventilation perfusion mismatch.105

Common Errors During Ventilation
Both excessive ventilation and hypoventilation can be harmful during CPR.6,11,12 After observing that patients in out-of-hospital cardiac arrest were ventilated on average at 37 times per minute in a clinical CPR device trial,6 animal studies were performed, which demonstrated that excessive ventilation rates were associated with a marked decrease in cerebral and myocardial perfusion pressures and markedly increased mortality.6 Similarly, after the first few minutes of CPR, the absence of periodic PPV reduces blood flow through the lungs secondary to collapse of both the bronchioles and the pulmonary vasculature.11 This can cause a profound decrease in cerebral oxygenation and perfusion.11,12 A correct balance between too little and too much ventilation is critical to neurologically favorable survival after cardiac arrest.6

Gasping and Coughing During CPR
Gasping occurs in some patients during CPR, especially if the medullary brainstem is perfused sufficiently to trigger the gasping reflex.107 Gasping during CPR is associated with more favorable outcomes.108,109 The so-called last gasp is associated with the development of negative intrathoracic pressure that in turn causes inspiration of air, enhances venous return to the heart, and decreases ICP, facilitating increased cerebral perfusion.109–111 Figure 3 demonstrates, in a pig model, the effect of gasping of cardiac arrest. In this example, a pig was being treated with active compression decompression (ACD) CPR and an impedance threshold device (ITD) when it began to gasp spontaneously during CPR. As shown, each gasp decreased intrathoracic pressure; decreased ICP; and increased carotid blood flow, aortic pressure, and the calculated CerPP.109 By contrast, PPV increased ICP.6 In these studies, right atrial pressure was measured, but flow back to the right heart was not measured. This figure helps to demonstrate how gasping increases CerPP by harnessing the thoracic pump to increase perfusion. The physiologic mechanism of benefit associated with gasping is somewhat similar to the physiology of cough CPR.112,113 Both work on a similar principle during the inspiratory portion of the cough as intrathoracic pressures are decreased.109,112 During the expiratory portion of a cough, intrathoracic pressures increase before the opening of the glottis. Cough CPR has been reported to maintain circulation and consciousness in patients in ventricular fibrillation for many minutes.112,114

Limitations of Conventional CPR
Under the best of clinical prehospital and in-hospital settings, the rate of survival with favorable neurological function after a cardiac arrest is <20% and <40%, respectively.1,25,115–118 The average rate of survival with good brain
function is only approximately 6% in those North American cities that study outcomes.3,29 As described earlier, the complex physiology of conventional S-CPR can be challenging to implement, but without the correct compression rate, compression depth, full chest recoil, lack of interruptions in CPR, and proper ventilation technique, outcomes are worse.5,6,12 Some of these challenges can be overcome with automated mechanical devices that have been shown to provide chest compressions that are at least equivalent to high-quality conventional manual CPR.119–121 By themselves, however, the use of automated CPR devices has not been shown to improve survival rates.115–121

Over the past several decades, study of the physiology of S-CPR has uncovered a number of inherent limitations, even when S-CPR is performed correctly.5,6,30,86 Recent progress has focused on ways to enhance the refilling of the heart after each compression, because S-CPR itself provides only 15% to 25% of normal cardiac output when performed perfectly.50,82,83 Understanding some of the limitations of S-CPR has resulted in several discoveries that hold promise of significantly enhancing cardiocerebral circulation during cardiac arrest.

Beyond Conventional S-CPR

Studies on CPR physiology have resulted in several fundamentally new approaches to improve outcomes after cardiac arrest. These include ways to harness the thoracic pump to enhance circulation to the heart and brain by transforming the thorax into an active pump to circulate more blood.21–24 The newly appreciated concept of intrathoracic pressure regulation (IPR) has resulted in innovative technologies and approaches to enhance perfusion, decrease ICP, and improve cardiac arrest outcomes.3,4,12,25,26,30,67,69,86,115,122–141

Additional discoveries associated with cardiac arrest include ways to reduce the potential for reperfusion injury, new insight into the potential importance of the position of the head during CPR, and methods to improve postresuscitation care. Essential for all of these potential advances is the need for the delivery of high-quality CPR in accordance with AHA guidelines.1 There has also been significant progress in incorporating multiple advances in the care of cardiac patients into a bundled approach to care. This has also resulted in a significant improvement in clinical outcomes.15,106,115

Intrathoracic Pressure Regulation Therapy

The concept of IPR is embodied in a number of noninvasive devices developed to regulate changes in intrathoracic pressure and to provide greater circulatory support than can be generated by S-CPR itself.12–14,67,82,83,115 IPR was inspired by the successful use of a household plunger, instead of a pair of hands, by someone attempting to resuscitate a family member in cardiac arrest.21 This index case resulted in a new method of CPR called ACD CPR.21 By repetitively pulling upward and pushing downward on the chest with a suction device, intrathoracic pressures increase and decrease, promoting greater ventilation and circulation than with S-CPR.21 Studies in animal showed that ACD CPR increased circulation during CPR but was insufficient by itself to maintain adequate ventilation.22,142,143 Further study of ACD CPR resulted in a discovery of the inspiratory ITD.23,24 By transiently impeding airflow into the lungs during the chest wall recoil or decompression phase of CPR, use of the ITD results in a significant reduction in intrathoracic pressure during S-CPR and ACD CPR.83,144 These mechanisms of action are shown schematically in Figure 4. By this means, the ITD significantly augments blood flow to the heart and brain during S-CPR, ACD CPR, and when used during CPR with automated devices.12,23,25,30,31,32,67,70,82,83,86,89,145–150 By transiently impeding gas flow into the lungs during the decompression phase of CPR, IPR therapy brings more blood back to the right heart and decreases ICP by decreasing intrathoracic pressure during the decompression phase of CPR.23,148 In this manner, use of the ITD during CPR mimics the gasping reflex as described earlier. Importantly, periodic PPV is required with the ITD, which can be attached to a facemask or advanced airway.

Over the past 2 decades, use of the ITD has been shown to significantly augment cerebral and myocardial perfusion in animals in cardiac arrest during S-CPR and ACD CPR and to improve hemodynamics in humans during S-CPR or ACD CPR.12,23,25,30,31,32,67,70,82,83,86,89,145–150 Further IPR research led to the development of a device able to provide a continuous negative intrathoracic pressure after each PPV.26,27 This more advanced active IPR approach has been used in animals and patients in cardiac arrest and non-cardiac arrest shock states.4,26,27,69,123,128,136,138,140,141,151

Conventional or Standard CPR and the Impedance Threshold Device

The ITD has been tested in animals and human subjects during S-CPR.26,31,83,86,106,115,147,149 The animal studies showed that the ITD increased blood flow to the heart and brain and improved survival with favorable neurological function.31,83,86,147,149 Subsequent testing in humans was also done.20,25,28,83,115,152 Most human trials showed a benefit of the ITD with S-CPR in terms of blood pressure or survival. However, the largest human trial, the National Institutes of Health Resuscitation Outcomes Consortium (ROC) Prehospital Resuscitation Impedance Valve and Early Versus Delayed Analysis (PRIMED) study compared a sham versus active ITD and early versus late analysis and defibrillation. The investigators reported no benefit of the ITD.29 In that trial, either a sham or active ITD, each with timing lights that flash 10 times/minute to guide ventilation rate, was tested in >8000 patients with out-of-hospital cardiac arrest treated with S-CPR.29 The sham device was designed to look, feel, and flash like the active ITD, but it did not impede the flow of respiratory gases into the lungs when the pressure in the thorax was subatmospheric. Only after the neutral results were published did the ROC PRIMED investigators report that there was a large variation in the compression rate and depth during the study.7,8 A third analysis by ROC investigators demonstrated that there was a statistically significant interaction between the quality of CPR delivered in the ROC PRIMED study and the effectiveness of the sham and active ITD.24 A subsequent independent reanalysis of the ROC PRIMED study similarly showed that the effectiveness of the active ITD was highly dependent on the quality of the S-CPR delivered.7,8,30,74
When chest compressions were delivered according to the recommendation of the AHA guidelines, then survival with favorable neurological function was significantly higher with the active ITD compared with the sham (Table 1). Taken together, these studies showed that there was a significant interaction between S-CPR quality metrics and the ITD.\(^7\)\(^8\)\(^74\)

With excessive chest compression rates or inadequate chest compression depth, the ITD was not effective.\(^30\) Conversely, when S-CPR was delivered according to the AHA recommendations, there was a significant 50% increase in the number of survivors with favorable neurological function (Table 1). Figure 5 demonstrates the importance...
of compliance with AHA guidelines and ITD effectiveness. The highest rates of survival with favorable neurological function were observed with compressions performed at rates around 100 per minute, a depth of 5 cm, and use of the active ITD. \(^{30}\) From a physiologic perspective, the discovery of these critical interactions among chest compression rate, depth, and inspiratory impedance helps to emphasize the potential benefit of IPR. \(^{30,153}\) These findings also highlight how critically important it is to remain compliant with CPR guidelines when performing CPR.

**Active Compression Decompression CPR and the Impedance Threshold Device**

The ITD was also assessed during ACD CPR in animals \(^{23,31,70,145,147,148}\) and in patients as the focus of 5 prospective randomized clinical trials. \(^{3,32–35}\) This device combination was shown to increase blood flow to the heart and brain and to improve survival with favorable neurological function. In the largest clinical trial, >2700 patients were randomly assigned to receive either S-CPR or the ITD + ACD CPR. \(^{3,36}\)

Patient survival to hospital discharge with favorable neurologic outcome, the primary study end point, was approximately 50% higher with the ITD + ACD CPR combination for patients with a cardiac arrest of presumed cardiac etiology \(^{3}\) (Table 2). Approximately 50% survival benefit relative to S-CPR was sustained for at least a year. \(^{3,36}\) Based on this trial, the combination of ACD CPR and the ITD was recently approved by the US Food and Drug Administration as the first CPR adjunct to increase the likelihood of survival after nontraumatic cardiac arrest. \(^{155}\)

**Advanced Intrathoracic Pressure Regulation**

The concept of push–pull ventilation has been adopted to enhance circulation and used for the treatment of cardiac arrest and shock. \(^{4,26,27,69,123,128,133,136,138,140,141,151}\) A series of devices have been designed to harness the changes in intrathoracic pressure to enhance venous return to the heart and circulate more blood to the brain and heart. \(^{4,26,27,69,123,124,127,128,133,136,138,140,141,151}\) They work as follows: After a positive pressure breath, respiratory gases are actively withdrawn from the lungs to generate

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**Table 1. Survival for Patients Receiving Acceptable Quality of CPR (Rate 80–120 per min, Depth 4–6 cm, Fraction ≥50%) in the National Institutes of Health Resuscitation Outcomes Consortium PRIMED Study**

<table>
<thead>
<tr>
<th>Survival to hospital discharge</th>
<th>Sham (n = 827), n (%)</th>
<th>Active (n = 848), n (%)</th>
<th>P</th>
<th>Relative Increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53/827 (6.4)</td>
<td>81/848 (9.6)</td>
<td>0.018</td>
<td>50</td>
</tr>
<tr>
<td>Discharge alive with mRS ≤3</td>
<td>34/827 (4.1)</td>
<td>61/848 (7.2)</td>
<td>0.0064</td>
<td>76</td>
</tr>
<tr>
<td>Witnessed arrest and discharge alive with mRS ≤3</td>
<td>25/421 (5.9)</td>
<td>50/419 (11.9)</td>
<td>0.0024</td>
<td>102</td>
</tr>
</tbody>
</table>

Chest compressions performed without interruptions for at least 50% of every minute.

CPR = cardiopulmonary resuscitation; mRS = modified Rankin scale.

*The compression fraction is the percentage of time the chest compressions are delivered continuously each minute.
negative intrathoracic pressure during the entire expiratory phase. The airway pressure curve and associated hemodynamics with this technology in a porcine preparation with hypovolemic shock are shown in Figure 6A and in cardiac arrest are shown in Figure 6B. This approach has been assessed in animals in cardiac arrest and in patients. When this approach is combined with S-CPR or ACD CPR, blood flow to the heart and brain is enhanced.

A device that provides this kind of IPR therapy, called the intrathoracic pressure regulator device (ITPR), has been approved for use in hypotensive patients by the Food and Drug Administration to enhance circulatory adequacy. In animals, brain blood flow is increased by approximately 50% with ACD + ITPR versus ACD + ITD. In humans, the use of S-CPR plus the ITPR significantly enhances circulation as measured by $\text{ETCO}_2$ during CPR and significantly increases the likelihood of successful resuscitation from 46% to 73%. However, research with this new approach is in its infancy. Further studies are needed to determine whether the use of the ITPR and similar devices that enhance venous return during the expiratory phase of CPR will result in improved long-term survival rates after cardiac arrest.

### Table 2. One-Year Survival with Good Neurologic Function, Defined as CPC ≤ 2, for All Patients in the ResQTrial

<table>
<thead>
<tr>
<th></th>
<th>S-CPR, n (%)</th>
<th>ACD + ITD, n (%)</th>
<th>P</th>
<th>Relative Increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT (n = 1655)</td>
<td>48/794 (6.0)</td>
<td>74/822 (9.0)</td>
<td>0.030</td>
<td>49</td>
</tr>
<tr>
<td>ITT (n = 2470)</td>
<td>68/1211 (5.8)</td>
<td>96/1233 (7.8)</td>
<td>0.062</td>
<td>34</td>
</tr>
</tbody>
</table>

ACD = active compression decompression; ITD = impedance threshold device; CPC = cerebral performance category; ITT = intention-to-treat population; patients met initial inclusion criteria for the study; mITT = modified intention-to-treat population; patients met initial and final inclusion criteria for the study including arrest of presumed cardiac etiology; S-CPR = standard cardiopulmonary resuscitation.

### Head-Up CPR

By convention, CPR has been performed for over a half a century with the patient in the supine position with the entire body on the same plane horizontal to the floor. Recent studies on the position of the head and body during CPR in pigs have demonstrated that elevation of the head during CPR has a profound beneficial effect on ICP, CerPP, and brain blood flow when compared with the traditional supine horizontal position. With the body supine and horizontal, each compression is associated with the generation of arterial and venous pressure waves that deliver a simultaneous high-pressure compression wave to the brain. With a patient’s head up, gravity drains venous blood from the brain back to the heart, resulting in a greater refilling of the heart after...
each compression, a lower compression phase ICP, and a substantial decrease in ICP, thereby reducing impedance to forward brain flow.\textsuperscript{14} By contrast, CPR with the patient’s feet up and head down resulted in a marked decrease in CerPP with a simultaneous increase in ICP\textsuperscript{14} (Fig. 1). As shown in cardiac arrest studies in pigs, elevation of the head results in an immediate decrease in ICP and an increase in CerPP.\textsuperscript{14} The effect of changing from the 0\degree horizontal to a 30\degree head up on key hemodynamic parameters during ACD + ITD is shown in Figure 1.\textsuperscript{14} Head-up CPR is ultimately dependent on the ability to maintain adequate forward flow. These benefits are realized only when an ITD is present; when the ITD is removed from the airway in these studies, systolic blood pressure and coronary and CerPP decrease rapidly.\textsuperscript{14} Currently, clinical studies are lacking. However, the new insight gained by these provocative animal studies suggest that elevation of the head during CPR may provide better cerebral protection and perfusion.

Reperfusion Injury Protection

Although nascent, the concept of postconditioning, or reperfusion injury protection, during CPR promises to provide additional benefit by reducing the potential for unintended damage in the first seconds to minutes of reperfusion after a prolonged ischemic insult.\textsuperscript{13,37,40,41,156,159}

It is well established that reperfusion injury can cause microvascular and endothelial dysfunction, reduce blood flow, and lead to end-organ metabolic dysfunction, cellular necrosis, and apoptosis.\textsuperscript{37,41,158–160} In a general sense, this concept also known as “postconditioning” can be defined as brief periods of reperfusion alternating with intentional reocclusion applied during the first minutes of reperfusion.\textsuperscript{37,158–160} This strategy need not be limited to mechanical alterations in hydrodynamics and may include pharmacological measures to accomplish similar objectives.\textsuperscript{13,37–43,163} Early animal studies are supportive of the importance of preventing reperfusion injury after prolonged cardiac arrest.\textsuperscript{37,157–159,161}

There are multiple ways to reduce or prevent reperfusion injury based on the putative mechanisms of action, which include ischemic postconditioning with intentional short periods of no flow after reflow, and pharmacologic agents, which activate reperfusion injury salvage kinase pathways or inhibit the opening of mitochondrial permeability transition pores.\textsuperscript{37} It is now clear that in the setting of a prolonged cardiac arrest, at least in pigs, reperfusion injury amelioration confers a significant benefit by preserving mitochondrial function.\textsuperscript{161}

More recent studies suggest that with reperfusion injury protection, the brain may be able to survive for well >15 minutes in the absence of any perfusion.\textsuperscript{39} Bartos et al.\textsuperscript{43} used multiple simultaneous interventions hypothesized to improve flow, reduce reperfusion injury, and accelerate cellular and vital organ recovery. Enhanced flow was provided with ACD + ITD CPR. Postconditioning was provided by 3 short intentional 20-second pauses and administration of sevoflurane, as reported previously by the same group to preserve mitochondrial respiration after prolonged ischemia and reperfusion.\textsuperscript{161,162} In addition, a synthetic surfactant, poloxamer 188 was administered to help seal nanosized holes in and between cells.\textsuperscript{163–168} Poloxamer 188 has been assessed previously in animals and humans to treat acute myocardial infarction and, more recently, in animals in cardiac arrest.\textsuperscript{43,167,168} Figure 7 demonstrates the impact of these multiple interventions on aortic pressure in a representative animal from that study.\textsuperscript{43} The authors found that more than half of the animals treated with this unique bundle were awake, alert, and functionally normal 48 hours after cardiac arrest. None of the control animals survived.\textsuperscript{43} These kinds of preclinical studies demonstrate the potential of these new approaches to markedly improve the likelihood of survival after cardiac arrest. Clinical studies are now needed to determine the potential added value of reperfusion injury protection after prolonged untreated cardiac arrest.
The Resuscitation Bundle

One lesson from the hundreds of different CPR studies that began in the early 1960s is that multiple treatments are needed for success in the chain-of-survival approach to the treatment of cardiac arrest.19,106,115 The most effective strategies have optimized circulation during CPR and reduced postresuscitation injury.19,106,115 The most effective resuscitation bundles to date include efforts to promote widespread use of bystander CPR, public access defibrillation, high-quality CPR by first responders and advanced life support providers, use of adjuncts that lower negative intrathoracic pressure during the decompression phase of CPR, and strategies that include postresuscitation revascularization and therapeutic hypothermia, or at least the prevention of fever.19,106,115 Such system-based approaches to resuscitation are based on a multipronged biophysical approach to significantly improve the likelihood for survival with restoration of neurological function after cardiac arrest.19,106,115,122,169

Currently, the bundled approach to prehospital care has significantly improved survival with good neurological function for all patients to as high as 20% in some cities and counties.19,115,118 Care is provided by highly trained prehospital personnel and specialized resuscitation hospitals.19,106,115 The greatest improvement has been in those patients who present with ventricular tachycardia where survival with restoration of neurological function is approximately 50%.19 These data are supportive of the progress in the field to date; they also reflect the challenges that persist for the 80% of patients who never wake up despite receiving conventional CPR.1,2,15,17–20,118

IS CPR OF BENEFIT AT ALL?

Given that survival rates after cardiac arrest have not changed much over the past half century since close chest manual CPR was first described, it is reasonable to ask whether CPR is really of benefit. This question was asked by Bardy,9 an expert in cardiac electrophysiology, who believes that early and effective defibrillation, and not CPR, is what is important. There is no doubt that defibrillators are important for resuscitating some patients in cardiac arrest who present with a rhythm that can be defibrillated. However, the incidence rate of ventricular fibrillation has been declining for the past 20 years170,171 and now is reported as the presenting rhythm for only between 20% and 35% of all out-of-hospital cardiac arrest.2,29 Given that the average cardiac arrest survival rate nationwide is <10%, one could argue that efforts to resuscitate patients in cardiac arrest are largely futile and that the millions of dollars spent on education and treatment strategies should be spent elsewhere. We will not settle that debate here, but this kind of challenge from Bardy9 and others is provocative and helps to stimulate potential breakthroughs. We believe that the early work described in this review on new ways to reduce reperfusion injury, new ways to protect the brain with head-up CPR, and aggressive postresuscitation care, including acute revascularization for patients in refractory ventricular fibrillation, are steps in the right direction.14,39,40 We speculate that over the next 50 years, these new ideas will be translated to meaningful changes in care and drive survival rates to higher levels than have been reported previously. Time will tell. Meanwhile, multiple emergency medical service (EMS) systems have already reported that by combining rapid and early defibrillation with high-quality CPR, ITD use, reperfusion injury protection strategies, and therapeutic hypothermia, overall survival rates with favorable neurological function can reach approximately 20% today and those with ventricular fibrillation are upward of 50%.19,115 In-hospital survival rates with favorable neurological function have been reported upward of 35%, and this includes patients with ventricular fibrillation, pulseless electrical activity, and asystole.122

PEDIATRIC CONSIDERATIONS

Cardiac arrest in the pediatric population presents some different challenges. Unlike in adults, common causes of pediatric cardiac arrest include respiratory arrest or drowning-induced asphyxia, prolonged shock from any cause, including trauma, and pre-existing cardiac disease that is usually congenital in nature.172

Severe bradycardia or asystole is the usual heart rhythm aberration to be dealt with. Ventricular arrhythmias are much less common (<10%) than in the adult population (>25%) and usually because of prolonged myocardial hypoxia.172 As with the adult population, survival from out-of-hospital cardiac arrest is significantly worse than in the in-hospital setting.122,172,173

To date, the experience with pediatric and adult rapid response teams on in-hospital CPR survival rates to discharge with good neurologic function has been mixed.174–176 Although the concept is appealing, a significant improvement in outcomes has not been demonstrated. Simulation experience supplemented by just-in-time and just-in-place training also hold promise to enhance outcomes even further, but to date, no definitive studies have shown a survival benefit.177–179 By consensus, the AHA child CPR guidelines apply to children from 1 year of age until puberty.180 For most pediatric patients, the age of 8 years correlates with a close approximation to the adult, from an anatomic and likely CPR physiologic perspective. In the younger patient, survival to discharge rates of in-hospital CPR are better than in those who are of school age or older.181–183

Several factors may be responsible for this, although it is postulated to be because of better CPR-induced blood flow, secondary to greater thoracic cage compliance.184 In addition, because most pediatric cardiac arrests are asphyxial/hypoxic in origin, rescue breathing with avoidance of hyperventilation and excessive positive airway pressure, in addition to prompt and uninterrupted chest compressions, is essential.44,45 As with the adult, open chest CPR provides about twice as much blood flow than S-CPR, but its use is almost always implemented when a thoracotomy of some kind is already performed, as in the operating room or pediatric intensive care unit postoperatively.185 Similar to adults, a pediatric resuscitation bundle is often used.186

As in adults, the use of post-CPR hypothermia is increasing, but its recommended duration and overall efficacy are somewhat controversial for all pediatric age groups.187,188 Studies have not unequivocally supported its use in the pediatric population. However, as with adults, most experts agree that hyperthermia, which is common in the pediatric post-CPR patient, must be avoided or managed aggressively when present.46,189

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Use of venoarterial extracorporeal membrane oxygenation as a rescue therapy in the pediatric population for treatment of prolonged cardiac arrest has been demonstrated to be useful in some patients, in particular in the postoperative cardiac surgical pediatric patient, when reversible cardiac dysfunction is present.47,48 However, as with adults, rigorous studies in this area are understandably lacking.47,48

CLINICAL IMPLICATIONS AND THE FUTURE
We remain in our infancy in understanding the complex physiology of cardiac arrest and CPR. However, similar to the treatment of other complex disease states, such as HIV infection, leukemia, or heart failure, we believe that we need to abandon the idea that there is a single “silver bullet” for the treatment of cardiac arrest, including defibrillation. In the case of HIV, 3 drugs found to be ineffective alone were shown to be highly effective when combined.190 We speculate that consistent and definitive advances in the treatment of cardiac arrest will require the synergy between multiple interventions in a bundle-of-care approach to this multifactorial disease state. Some of these potential interventions are summarized in Table 3.

Within the past decade, it has become clear, as we have said that there is no single magic bullet for patients in cardiac arrest. Cardiac arrest is best treated with a multipronged approach based on the physiologic and biochemical first principles. These include optimization of circulation and postresuscitation organ recovery and minimization of reperfusion injury and common errors during CPR delivery. The recognition that common errors in CPR delivery are prevalent and often lethal has resulted in a “back-to-basics” approach to education and delivery of basic CPR. The frequency of errors during CPR has also resulted in a better understanding of the needs for and benefits of feedback tools and automated CPR devices to assure that correct rate, depth, and full recoil are achieved.119–121 None of these new approaches is exceptionally difficult to implement. We anticipate that once many of them have been scientifically verified and combined with current system-based approach to care, the potential to successfully and fully resuscitate many patients who we cannot help with current management seems to be well within our reach.

DISCLOSURES

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Contribution: This author helped prepare the manuscript.
Attestation: Keith G. Lurie approved the final manuscript.
Conflicts of Interest: Keith G. Lurie is a consultant for Zoll Medical and coinventor of the impedance threshold device and the active compression decompression CPR device.

Table 3. Potential Ways to Improve Outcomes During CPR

<table>
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<tr>
<th>CPR devices</th>
<th>Optimize perfusion</th>
<th>Minimize cellular permeability</th>
<th>Restore blood–brain barrier</th>
<th>Optimize intracellular metabolism and biochemistry</th>
<th>Minimize postresuscitation injury cascades</th>
</tr>
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<tbody>
<tr>
<td>arterial</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>venous</td>
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CPR = cardiopulmonary resuscitation.

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Name: Edward C. Nemergut, MD.
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Contribution: This author helped prepare the manuscript.
Conflicts of Interest: Michael Sweeney is coinventor of the impedance threshold device.
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