Chapter 41: Cardiopulmonary Arrest

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 7, Cardiac Arrest.

KEY CONCEPTS

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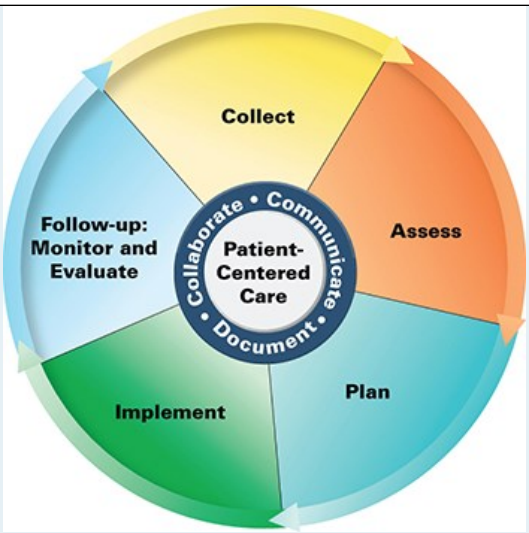
1. High-quality cardiopulmonary resuscitation with minimal interruptions in chest compressions should be delivered to all patients following cardiac arrest.
2. The American Heart Association (AHA) algorithm for basic life support emphasizes circulation, airway, and breathing, forming the mnemonic "CAB."
3. The purpose of using vasopressor therapy following cardiac arrest is to augment coronary and cerebral perfusion pressures.
4. Successful treatment of both pulseless electrical activity (PEA) and asystole largely depends on determining the underlying cause. Epinephrine should be administered as soon as possible.
5. Following the return of spontaneous circulation (ROSC) from a cardiac arrest, patient management should be directed toward the postcardiac arrest syndrome. Post-resuscitation care often requires several interventions including, but not limited to, targeted temperature management, stabilization of respiratory and cardiovascular systems, interventions to achieve hemodynamic stability, control of blood glucose, and treatment of seizures and infectious complications.
6. Intravenous (IV) administration is the preferred route for medication delivery; intraosseous (IO) can be considered when IV access cannot be readily obtained or is not feasible.

PATIENT CARE PROCESS

Patient Care Process for Cardiac Arrest



Collect*

- Patient characteristics (eg, sex, age)
- Patient medical history (if available)
- Current and past medications that could have contributed to the arrest or serve as a clue to the underlying medical history
- Objective data
  - Presence of a pulse
  - Cardiac rhythm

Assess*

- Is the patient responsive?
- Is there a pulse present?
- Are the electrocardiogram (ECG) leads correctly placed on the patient?
- Is the rhythm shockable?

Plan*

- Activate emergency medical services (EMS) and obtain an automated external defibrillator (AED) if one is nearby (for out-of-hospital arrest) (Fig. 41-2)
- Call for “code blue” and obtain crash cart (for in-hospital arrest)
- Immediately begin chest compressions and follow basic life support (BLS) algorithm
- Administer electrical therapy (ie, defibrillation) if indicated
- Drug therapy per advanced cardiac life support (ACLS) algorithm if indicated (Table 41-1)
- Monitor for the return of spontaneous circulation (ROSC), cardiac rhythm, and pulse

Implement*

- Perform high-quality chest compressions with minimal interruptions
- Administer defibrillations and drug therapy as indicated by cardiac rhythm

Follow-up: Monitor and Evaluate*

- Monitor end-tidal CO_2 as an indicator of cardiopulmonary resuscitation (CPR) quality
- Implement postresuscitative care plan
- ECG and percutaneous coronary intervention (PCI) when an acute coronary syndrome is suspected
- Review patient history for identification of other contributors or underlying cause of the arrest
- Diligent monitoring of blood pressure, oxygen saturation, temperature, urine output, and glucose
- Evaluate and monitor for seizure

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Review the American Heart Association (AHA) algorithms for BLS and ACLS. Create a table that lists the medications used during a cardiac arrest and after the ROSC, when those medications might be used, and the intended purpose of each medication. All guidelines for cardiopulmonary resuscitation and emergency cardiac care can be found at https://tinyurl.com/zy2efpq.

INTRODUCTION

Cardiac arrest is defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation (eg, a detectable pulse, unresponsiveness, and apnea).[1] While there is wide variation in the reported incidence of cardiac arrest, there are more than 350,000 people in the United States who are assessed by EMS for a suspected out-of-hospital cardiac arrest each year.[1] Survival to hospital discharge following out-of-hospital cardiac arrest is only 10.5% and survival with good neurologic function is even lower.[1] While there has been a minimal change over the last 40 years, the survival rate for out-of-hospital cardiac arrest improved slightly during the last reported observation period between 2005 and 2012.[2] This improvement was seen in both prehospital and in-hospital survival.

The incidence of in-hospital cardiac arrests is roughly 10 per 1,000 hospital admissions in the United States annually.[1] Similar to out-of-hospital arrests, some progress has also been made over the past decade with in-hospital cardiac arrests, where survival rates to hospital discharge have increased from 17% in 2000 to 27% in 2019.[1] Survival rates are substantially higher in victims with a shockable rhythm (ie, those who are treated with electrical defibrillation).

EPIDEMIOLOGY

Cardiac arrest can arise from either cardiac or noncardiac origins (eg, submersion, asphyxia, trauma, and overdose). In adult patients, cardiac arrest usually results from the development of an arrhythmia. Historically, ventricular fibrillation (VF) and pulseless ventricular tachycardia (PVT) have been the most common initial rhythms seen in out-of-hospital arrests, but these are now seen in less than one-quarter of cases.[1] In fact, data from the Cardiac Arrest Registry to Enhance Survival (CARES) project reported asystole to be the most common presenting rhythm (53%), which is similar to

other registry data whereby nonshockable rhythms (ie, asystole, PEA) were more prevalent.[3] It is unclear why there has been a change in the types of arrhythmias that most commonly lead to cardiac arrest. Possible explanations include the increasing incidence of noncardiac causes of arrest that present with apnea leading to bradycardia and then pulseless electrical activity (PEA) or asystole. A second explanation might be the increasing role of implantable pacemakers and defibrillators.[4] Finally, beta-blockers and ACE inhibitors may shorten the duration of VF, and the expanded use of these drug classes for ischemic heart disease and heart failure may account for the increased occurrence of non-VF/PVT rhythms.[4] This change in the presenting rhythm types is concerning because survival rates to hospital discharge are substantially higher with shockable rhythms like VF and PVT (26%) compared to nonshockable rhythms like PEA (10%) and asystole (2%).[3]

A similar finding has been observed with in-hospital cardiac arrest. One study using the "Get With The Guidelines-Resuscitation" registry reported that 79% of patients had an initial rhythm of asystole or PEA and only 21% had VF or PVT.[5] Survival rates were 12.2% for asystole/PEA and 35% for VF/PVT.

In pediatric patients, cardiac arrest typically results from respiratory failure and asphyxiation. As such, the initial rhythm most often encountered in out-of-hospital arrest is PEA or asystole. Similar to the adult population, survival rates have increased over the past decade from 28% in 2000 to 52% in 2019 according to one registry.[1] Survival rate with out-of-hospital pediatric arrests is roughly 15% and is lower in infants when compared to children and adolescents.[1] Survival following in-hospital cardiac arrest is much higher (45%), and most survivors have a favorable neurologic outcome (89%).[6]

ETIOLOGY

The most common clinical finding in adult patients who suffer cardiac arrest is coronary artery disease, accounting for roughly 75% of sudden cardiac deaths.[7] Other causes of sudden cardiac death include cardiomyopathies, valvular heart disease, myocarditis, left ventricular hypertrophy, primary electrical heart disease, and noncardiac causes. Unfortunately, in many patients (up to 69%), cardiac arrest is the first clinical sign of coronary artery disease with no preceding signs or symptoms.[7]

In pediatric patients, cardiac arrest is often the terminal event of respiratory failure or progressive shock.[8] Out-of-hospital cardiac arrests frequently are associated with trauma, sudden infant death syndrome, drowning, poisoning, choking, severe asthma, and pneumonia. In-hospital cardiac arrests, on the other hand, are associated with sepsis, respiratory failure, drug toxicity, metabolic disorders, and arrhythmias.

PATHOPHYSIOLOGY

There are two distinct pathophysiologic conditions associated with cardiac arrest. The first is primary cardiac arrest whereby arterial blood is fully oxygenated at the time of arrest. As forward blood flow ceases, arterial blood oxygenation remains normal for about 10 minutes and subsequently declines due to the lack of ventilation.[9] Alternatively, respiratory failure can lead to severe hypoxemia, hypotension, and secondary cardiac arrest. It is important to identify the underlying pathophysiology as different treatment approaches are required.[9]

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Cardiopulmonary Arrest

General:

- Cardiac arrest is characterized by the cessation of cardiac mechanical activity. General signs and symptoms are consistent with a sudden cessation of circulation.

Symptoms (occurring prior to the event)

- Anxiety
- Crushing chest pain
- Nausea
- Vomiting
- Diaphoresis

Signs

- Apnea
- Hypotension
- Lack of a detectable pulse
- Cyanosis
- Cold, clammy extremities
- Loss of consciousness
- Syncope

TREATMENT

Desired Outcome

The global goals of resuscitation are to preserve life, restore health, relieve suffering, limit disability, and respect the individual's decisions, rights, and privacy.[10] Providing high-quality CPR and quickly achieving the ROSC with effective perfusion and ventilation can minimize hypoxic damage to vital organs and achieve these goals. Survival to hospital discharge with good neurologic function should be the primary treatment outcome sought by clinicians. Survival to hospital discharge in a vegetative or comatose state cannot be classified as a success and can impose a tremendous economic burden on the healthcare system.

The presence of a healthcare advanced directive allows patients to communicate their wishes and preferences regarding medical care and may lead to a "do not attempt resuscitation" order. These orders should explicitly state the resuscitation interventions that are to be performed and should have been clearly communicated by the patient, their family, or a surrogate decision-maker.

General Approach to Treatment

Cardiopulmonary Resuscitation

Resuscitation techniques have been studied for many years. In 1960, Kouwenhoven described positive outcomes in 14 of 20 patients with in-hospital

cardiac arrest who were given closed chest compressions at a rate of 60 per minute.[11] Following the publication of this landmark article, chest compressions integrated with expired air ventilation (ie, mouth-to-mouth) became the fundamentals of basic life support known as the "ABC's."[11]

Cardiopulmonary resuscitation employs chest compressions to restore threshold blood flows, particularly to the heart and brain. There are two proposed explanations to describe how chest compression improves blood flow during CPR.[11] The original explanation is known as the cardiac pump theory whereby compression of the heart between the sternum and vertebrae creates forward flow. However, echocardiography during chest compressions has revealed that the left ventricular size does not always change and the mitral valve may not close.[11] The second explanation is the thoracic pump theory whereby intrathoracic pressure changes during chest compressions promote blood flow while the heart merely acts as a passive conduit. It is likely that both cardiac compression and intrathoracic pressure changes contribute.

Since 1966, the AHA has published guidelines for the treatment of cardiac arrest in 5-year increments. In 2015, this process transitioned to an online format that is continuously updated in an attempt to expedite the most current evidence-based practices to the bedside. The most recent document, the 2020 guidelines, reflects alignment with the International Liaison Committee on Resuscitation and reviews scientific questions considered of greatest significance and new evidence.[12]

1 High-quality CPR continues to be emphasized in the latest guidelines published by the AHA. Clinicians must focus on proper technique, including adequate rate and depth of compressions, allowing full chest recoil after each compression, avoiding excessive ventilation, and minimizing interruptions. There is an association between survival to hospital discharge and chest compression rate (optimally between 100 and 120 beats/minute), chest compression depth (optimally 40-54 mm), and chest compression fraction (optimally the proportion of resuscitation time without spontaneous circulation when chest compressions are administered should be ≥60%).[13] Unfortunately, the provision of CPR is frequently sub-optimal, particularly when rescuers become fatigued.[14] Real-time audiovisual feedback mechanisms during CPR have been encouraged. These can include voice prompts (eg, "push harder"), visual displays (for compression quality), audio prompts (eg, metronome to guide CPR rate) or an analog "clicker" feedback device that emits a noise and sensation when sufficient pressure is applied during CPR. One study reported a 25% absolute increase in survival to hospital discharge with the use of an analog "clicker" device.[15]

The 2020 guidelines continue to emphasize the "chain of survival" to highlight the treatment approach and illustrate the importance of a timely response. The updated guidelines include two separate chains (one for out-of-hospital cardiac arrest and another for in-hospital cardiac arrest), both having six links.[16] The two chains reflect the differences in the steps needed to respond to a cardiac arrest in the in-patient and out-patient settings. The links in each chain of survival are as follows:

Out-of-hospital

1. Activation of emergency response
2. High-quality CPR
3. Defibrillation
4. Advanced resuscitation
5. Postcardiac arrest care
6. Recovery

In-hospital

1. Early recognition and prevention
2. Activation of emergency response
3. High-quality CPR
4. Defibrillation

5. Postcardiac arrest care

6. Recovery

Activation of emergency response systems and early recognition and prevention are the first links in the chain of survival for out-of-hospital and in-hospital cardiac arrests, respectively. For out-of-hospital cardiac arrests, activation of emergency response systems allows for dispatcher-assisted CPR whereby instructions are delivered to a community bystander over the telephone. Further, mobile phone technology is increasingly being used to summon nearby bystanders who might assist with out-of-hospital events. For in-hospital cardiac arrests, clinical deterioration typically precedes a cardiac arrest; therefore, early warning systems based on vital sign abnormalities, advanced scoring systems, or staff concerns are advised.[17] High-quality CPR and rapid defibrillation for shockable rhythms are the foundation for good resuscitation outcomes after cardiac arrest.[18] Advanced resuscitation interventions, which include pharmacotherapy, advanced airways, and extracorporeal CPR, may improve outcomes in special situations. Postcardiac arrest care consists of important therapies such as targeted temperature management, mechanical ventilation, and other crucial critical care support modalities including pharmacotherapy. Recovery is the newest link added to both chains of survival. Recognizing that recovering from cardiac arrest continues long after hospital discharge, measures to support physical, cognitive, emotional well-being, and psychosocial needs are recommended.[16]

Sequence of Resuscitation

Basic Life Support

The mnemonic for the CPR sequence is “CAB” which stands for circulation, airway, and breathing. Historically, BLS and ACLS providers have been taught the mnemonic, “ABC.” The change to CAB was made to stress the importance of maintaining blood flow to the heart and brain and to avoid delays or interruptions to chest compressions.

When first encountering a cardiac arrest victim, the initial action is to determine if the patient is responsive. If there is no response, the rescuer should immediately activate the EMS team, obtain (or call for) an AED, and then immediately start CPR with chest compressions. A cardiac arrest victim will be unresponsive, and it can be difficult for rescuers to determine if the victim is breathing normally. Thus, “look, listen, and feel” for respirations is no longer recommended as part of the initial assessment.[16] Similarly, lay rescuers may have difficulty in detecting a pulse leading to delays in chest compressions; thus, a pulse check is not recommended. In situations where the rescuer is unsure if the victim has suffered a cardiac arrest (eg, when agonal breathing is present), CPR should be promptly initiated. The risk of chest compressions in a patient who is not in cardiac arrest is low compared to the high potential for harm should CPR be withheld in a pulseless victim.[16] Healthcare providers could assess for a pulse but take no more than 10 seconds to do so. If one is not detected within this short time frame, then chest compressions should be immediately initiated.[16]

The prompt provision of chest compressions is of paramount importance, and rescuers should attempt them regardless of rescuer experience or skill. High-quality chest compressions should be delivered at a rate of 100 to 120 compressions per minute, with adequate depth (at least 2 in. [~50 mm] in an adult), while allowing full chest recoil and minimizing any interruptions.

While the provision of high-quality chest compressions is essential, the role of ventilation (ie, rescue breaths) in the initial management of cardiac arrest is less clear. Chest compressions deliver a small but critical amount of oxygen to the brain and myocardium. Cerebral and coronary perfusion pressure (CPPs), however, build up slowly once chest compressions are begun. These perfusion pressures are lost if chest compressions are stopped to deliver mouth-to-mouth ventilation resulting in reduced blood flow and decreased effectiveness of CPR. In fact, the time it takes to deliver two rescue breaths has been reported to range between 10 seconds and 16 seconds based on the experience of the rescuer.[19] These interruptions can be significant given the proportion of time chest compressions are being performed during CPR is associated with improvements in survival.[20] Along with concerns related to interruptions with chest compressions, some lay rescuers may be reluctant to initiate CPR at all, if they are uncomfortable with administering rescue breaths. These principles led to the origin of chest compression-only CPR. Chest compression-only CPR has been associated with increased survival compared to conventional CPR and no bystander CPR.[21] However, if ventilations are withheld, arterial oxygen content will decrease as CPR duration increases.

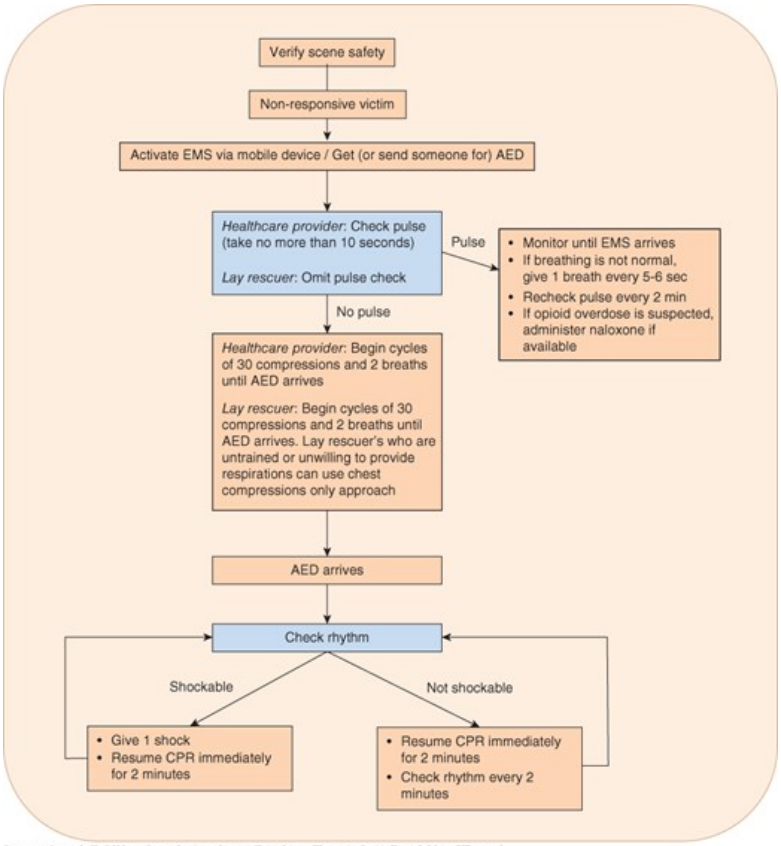
Based on a recent systematic review, CPR recommendations have been updated.[16,22] Chest compression-only CPR is appropriate for lay rescuers who

are untrained or unwilling to provide respirations. Lay rescuers who are trained, able, and willing to give rescue breaths should do so using a compression to breath ratio of 30:2. For EMS-delivered CPR, providers should perform CPR in cycles of 30 compressions and 2 breaths or alternatively 1 breath every 6 seconds for asynchronous ventilation during continuous chest compressions.

In all cases, CPR should continue until an AED arrives. The AED leads should be immediately placed on the victim so that the device can determine if the rhythm is shockable. If so, then one shock should be delivered, and CPR immediately resumed for 2 minutes or until prompted by the AED for another rhythm check. If the rhythm is not shockable, CPR should resume immediately for 2 minutes or until prompted by the AED. This cycle should be continued until advanced life support providers take over or the victim starts to move (Fig. 41-1). In settings where more than one rescuer is present, rotating the provider performing chest compressions should occur every 2 minutes to minimize rescuer fatigue, which can lead to poor quality chest compressions.

FIGURE 41-1

Treatment algorithm for adult cardiac arrest: Basic life support (BLS).



Defibrillation is crucial for survival in cardiac arrests caused by VF or PVT, especially when administered as soon as possible after the onset of the arrest. When the duration of VF/PVT is more prolonged (eg, an unwitnessed or an unmonitored arrest due to the arrival of an AED), the efficacy of defibrillation is compromised due to depletion of myocardial oxygen reserves and the presence of global tissue ischemia. A short period of CPR to replenish blood flow (via chest compressions) and "flush out" deleterious metabolic factors may be beneficial. Intentional, prolonged periods of chest compressions (90-180 seconds) before defibrillation have not been shown to improve outcomes.[22] Therefore, in unmonitored cardiac arrests, a brief period of CPR can be administered while the defibrillator is being obtained and readied for use.

CPR can be physically demanding, and rescuer fatigue can lead to poor quality chest compressions. As a result, mechanical devices have been developed with the aim of providing consistent high-quality chest compressions that can be sustained throughout the entire arrest period. Animal studies have shown that cerebral blood flow is greater with these devices compared to manual compression. Studies in humans, however, have not demonstrated improved survival or survival with good neurological function.[16] Lack of survival benefit may be due to time delays associated with their

deployment. While the routine use of mechanical CPR devices is not recommended, their use may be considered in specific settings where the delivery of high-quality manual compressions may be challenging such as ambulance or helicopter transfers.

Advanced Cardiac Life Support

Once EMS- or other ACLS-certified providers arrive, additional therapy may be given. Either a bag-mask device or an advanced airway such as a supraglottic device or an endotracheal tube may be utilized to provide ventilation. If an advanced airway is used, supraglottic airways are preferred in settings with low tracheal intubation success rates or when minimal training opportunities exist. Once an airway is established, one provider can deliver 1 breath every 6 seconds while continuous chest compressions are being performed by a second provider.

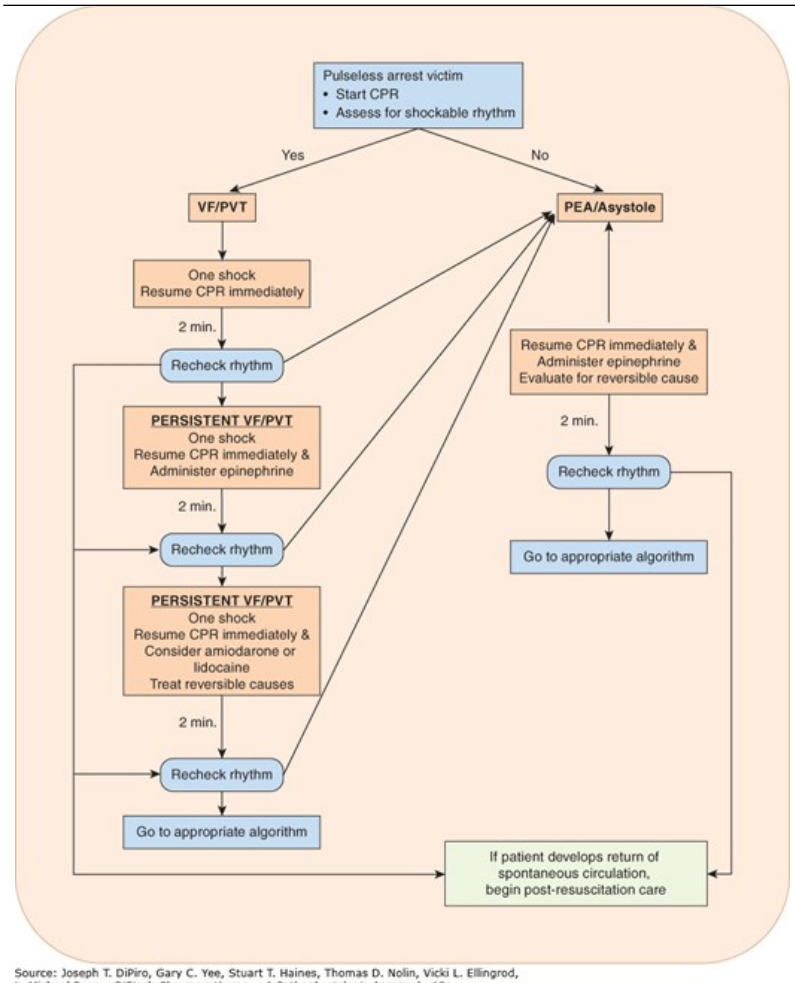
Monitoring of CPR quality may be performed using end-tidal carbon dioxide ($ETCO_2$) monitoring or arterial blood pressure assessment when feasible. $ETCO_2$ is the concentration of carbon dioxide in exhaled air at the end of expiration. During cardiac arrest, the level of $ETCO_2$ decreases because there is no flow through the pulmonary circulation. Thus, a persistently low $ETCO_2$ (ie, <10 mm Hg [1.3 kPa]) during CPR in intubated patients makes ROSC unlikely.[16] One large study using the "Get with the Guidelines-Resuscitation" registry reported a higher rate of ROSC when physiologic monitoring with either $ETCO_2$ or arterial blood pressure was performed.[23] Physiologic monitoring with $ETCO_2$ or arterial blood pressure is, therefore, suggested.

If not already placed, an AED should be attached and access for administration of parenteral medications should be obtained. Cardiac arrest victims who are in VF or PVT should be administered one shock with the immediate resumption of chest compressions.[16] If there is still a shockable rhythm, then an additional shock should be delivered every 2 minutes. After two cycles, epinephrine is indicated. Chest compressions continue while medications are being prepared and administered. This cycle is repeated until either a pulse is obtained with effective circulation, the rhythm changes or the patient expires. If the cardiac rhythm is not deemed to be shockable, then the patient is likely to be in either asystole or PEA. In this circumstance, epinephrine should be administered as soon as possible and the rescuer must consider reversible causes (Fig. 41-2).

Extracorporeal CPR is the use of cardiopulmonary bypass during the resuscitation of a cardiac arrest victim. It entails the rapid deployment of veno-arterial extracorporeal membrane oxygenation (ECMO) to provide circulatory support when conventional CPR is unsuccessful. The goal is to provide end-organ support while reversible conditions are addressed. ECMO is a highly specialized therapy that requires a dedicated team of specialized experts. While there is insufficient evidence to support the routine use of extracorporeal CPR, it may be considered as rescue therapy if there is a reversible cause of the arrest.

FIGURE 41-2

Treatment algorithm for adult cardiac arrest: Advanced cardiac life support (ACLS).



Ventricular Fibrillation/Pulseless Ventricular Tachycardia

Nonpharmacologic Therapy

Ventricular fibrillation and PVT are "shockable rhythms." Thus, defibrillation combined with cardiopulmonary resuscitation are crucial components in the care of cardiac arrest victims. CPR provides critical blood flow to the heart and brain, prolongs the time VF/PVT is present (prior to the deterioration to asystole), and increases the likelihood that a shock will terminate VF/PVT and result in a rhythm compatible with life. The brain can normally survive for only 3 to 5 minutes before damage occurs; thus, delays in the provision of CPR can worsen outcomes. With immediate CPR, the rate of survival decreases by 3% to 4% per minute between the onset of the arrest and defibrillation.[24] Without bystander CPR, survival rates decrease by 7% to 10% per minute.[24] In effect, CPR can increase the likelihood of survival threefold from arrest to survival. Basic CPR alone is not likely to terminate VF/PVT; electrical defibrillation is often necessary to restore a cardiac rhythm.

Pre-hospital systems of care remain an area of emphasis for communities to improve outcomes following a cardiac arrest.[18,25] In one large study, the rate of bystander CPR was only 34% while only 2.3% of cardiac arrests utilized an AED.[26] Community programs are necessary to provide education and raise awareness of the importance of early CPR. Examples of these programs include dispatcher-assisted CPR, whereby instructions are provided via mobile telephone. Mobile phone technology can also be used to alert a bystander that an arrest has occurred within their geographic vicinity. Education programs on the use of public access defibrillators can promote the early use of AEDs by lay responders. One systematic review reported survival rates of 53% with the early use of defibrillation using an AED administered by lay responders.[27] Finally, specialized cardiac arrest centers with experienced clinicians who are well versed in the evidence-based management of post-resuscitation care could be important. While data reporting improvements in survival to hospital discharge are mixed, these centers often have the capability to perform ECMO and other advanced forms of organ

support.

Pharmacologic Therapy

Vasopressors

Vasopressors continue to be the first pharmacologic agents administered in the setting of cardiac arrest despite limited evidence demonstrating improvements in neurologic function postarrest. Nevertheless, vasopressors have been associated with an increased rate of ROSC and play a major role in the pharmacotherapy of cardiac arrest.

3 The primary goal of vasopressor therapy is to augment low coronary and cerebral perfusion pressures encountered during CPR. Chest compressions can improve blood flow to the heart and the brain but only to about 25% of normal. Even with optimally performed chest compressions, CPPs are only 10 to 15 mm Hg, and systolic arterial pressure is rarely above 80 mm Hg.[28] Clinical data have indicated that ROSC is unlikely when the CPP is less than 15 mm Hg.[29,30] Vasopressors, therefore, work to increase these pressures through their vasoconstrictive properties.

Epinephrine continues to be the drug of first choice for the treatment of VF, PVT, asystole, and PEA. Epinephrine is an alpha- and beta-receptor agonist causing vasoconstriction as well as increasing the rate and forcefulness of heart contractions.

In a large randomized controlled trial of patients with out-of-hospital cardiac arrest (18% with VF or PVT), epinephrine was compared to saline placebo.[31] Epinephrine use was associated with a significant improvement in survival at 30-days, and the benefit was more pronounced in patients with a nonshockable initial rhythm. Favorable neurologic outcome (at discharge), however, was no different in the epinephrine group. In fact, there were more patients with severe neurologic impairment with epinephrine. A second randomized, controlled trial compared epinephrine with placebo in patients with cardiac arrest (fewer than 50% had VT or PVT as the initial rhythm).[32] ROSC and survival to hospital admission were significantly higher with epinephrine but there was no difference in survival to hospital discharge. Similar to the previous trial, the effect of epinephrine was greater in those with non-shockable rhythms. A subsequent meta-analysis found that epinephrine was associated with significant improvements in ROSC, survival to hospital discharge, and survival at 30 days.[33] There was no difference, however, in neurological outcome at discharge. When stratified by initial rhythm, these differences were greater in the cohort of patients with nonshockable rhythms. Most notably, survival at 30-days was significant with nonshockable rhythms but not with VF/PVT.

Several large observational studies have evaluated the impact of epinephrine on survival. One large registry study failed to demonstrate a survival benefit with prehospital administration of epinephrine.[34] Despite a significant improvement in ROSC with epinephrine, 1-month survival and survival with good neurologic function were both lower in patients who received epinephrine. A second study evaluated outcomes in patients with witnessed out-of-hospital cardiac arrest.[35] Epinephrine was associated with improvements in survival at 1 month or discharge in patients with VF/PVT but there was no difference in neurologically intact survival.

Timing of epinephrine administration could be an important confounder and contribute to the heterogeneity observed with survival data. In a posthoc analysis of data from the largest randomized controlled trial conducted to date, the odds of ROSC decreased in both epinephrine and placebo groups over time, but at a greater rate with placebo.[36] A second study revealed survival and favorable functional status decreased with delayed administration.[37] Specifically, ROSC was highest in the cohort who received epinephrine within 5 minutes after the provision of advanced life support. Similarly, other studies have reported the association with delays in epinephrine administration and a reduction in the odds of survival and the odds of hospital discharge with good neurologic function are reduced.[38-42]

Despite notable improvements in survival, epinephrine does not improve survival with good neurologic function, which may be related to its mechanism of action. Epinephrine causes alpha-mediated vasoconstriction which increases coronary perfusion but may also decrease perfusion to other vital organs. Animal research has linked epinephrine to a decrease in cerebral microvascular blood flow and an increase in brain tissue ischemia during and after CPR.[43] One study in humans measured cerebral oxygenation in patients who experienced an in-hospital cardiac arrest, before-and-after epinephrine administration.[44] A small increase in cerebral oxygenation (1.4%) was noted but the clinical importance of this small change is questionable. Alternatively, the negligible effect on neurologic function could be due to the brain being more sensitive to ischemia compared to other organs and less able to recover once ROSC is achieved.

Epinephrine also stimulates beta-receptors, which can increase myocardial oxygen demand, impair lactate clearance, and contribute to post-resuscitation myocardial dysfunction.[45] Studies have compared epinephrine with other adrenergic agonists with less beta-activity (eg, pure alpha-1 agonists such as phenylephrine and methoxamine or more potent alpha-agonists like norepinephrine).[46] When compared to pure alpha-1 agonists, there is no advantage in terms of long-term survival. One potential reason could be the potent alpha-2 effects of epinephrine and the fact that these receptors lie extrajunctionally in the intima of the blood vessels making them more accessible to circulating catecholamines. Furthermore, during ischemia, the number of postsynaptic alpha-1-receptors decreases which suggests a greater role for alpha-2 agonists during CPR. Epinephrine has also been compared with norepinephrine, a potent alpha-agonist (both alpha-1 and alpha-2) with some beta-1 effects. In the only large-scale randomized, double-blind, prospective trial comparing epinephrine and norepinephrine use in patients with an out-of-hospital cardiac arrest, there were no significant differences in ROSC, hospital admission, or discharge.[47] A second, smaller study demonstrated higher resuscitation rates with norepinephrine compared to epinephrine (64% vs 32%) but no significant difference in survival to hospital discharge.[48]

The recommended dose for epinephrine is 1 mg administered by intravenous (IV) or intraosseous (IO) injection every 3 to 5 minutes[16] (Table 41-1). The recommended dose for epinephrine was derived from animal studies (0.1 mg/kg in a 10 kg dog) and equates to approximately 0.015 mg/kg for a 70 kg human.[49] Animal studies have demonstrated a positive dose-response relationship with epinephrine, suggesting that higher doses might improve hemodynamics and resuscitation success.[46] However, human studies have reported increased morbidity with high-dose epinephrine. The hemodynamic findings are consistent with catecholamine toxicity, including decreased cardiac indices, left ventricular dysfunction, and decreased oxygen delivery. This discrepancy between animal and human studies could be related to most victims of cardiac arrest having coronary artery disease, which is not encountered in an animal model. Additionally, atherosclerotic plaques in humans can aggravate the balance between myocardial oxygen supply and demand, and the interval from arrest to treatment is longer in human studies than that encountered in an animal model. Thus, high-dose epinephrine is not recommended for routine use in cardiac arrest.

TABLE 41-1

Evidence-Based Recommendations

Recommendations	Recommendation Grades[a]
Epinephrine	
Epinephrine is recommended for patients in cardiac arrest	Class I, LOE B-R
Standard dose epinephrine (1 mg IV/IO every 3-5 minutes) may be reasonable for patients with cardiac arrest	Class IIa, LOE B-R
In patients with cardiac arrest with a shockable rhythm, it may be reasonable to administer epinephrine after initial defibrillation attempts have failed	Class IIb, LOE C-LD
In patients with cardiac arrest with a nonshockable rhythm, it may be reasonable to administer epinephrine as soon as feasible after the onset of cardiac arrest	Class IIa, LOE C-LD
High-dose epinephrine is not recommended for routine use in cardiac arrest	Class 3, LOE B-R
Vasopressin	
Vasopressin alone or in combination with epinephrine may be considered but offers no advantage as a substitute for standard dose epinephrine	Class IIb, LOE C-LD
Amiodarone	
Amiodarone may be considered in patients with VF/PVT unresponsive to defibrillation	Class IIb, LOE B-R
Lidocaine	
Lidocaine may be considered in patients with VF/PVT unresponsive to defibrillation	Class IIb, LOE B-R
Magnesium	
Magnesium is not routinely recommended for VF/PVT	Class III: No benefit, LOE B-R
Thrombolysis	
Thrombolysis may be considered when cardiac arrest is suspected to be caused by pulmonary embolism	Class IIb, LOE C-LD
Sodium bicarbonate	
Routine use of sodium bicarbonate is not recommended	Class III: No benefit, LOE B-R
Corticosteroids	
For out-of-hospital cardiac arrest, use of corticosteroids during CPR is of uncertain benefit	Class IIb, LOE C-LD

CPR, cardiopulmonary resuscitation; IV, intravenous; IO, intraosseous; VF, ventricular fibrillation; PVT, pulseless ventricular tachycardia; LOE, level of evidence.

[a]Key for evidence-based classifications:

Class of recommendations:

- Class I (Strong). Benefit >>>Risk
- Class IIa (Moderate). Benefit >> Risk
- Class IIb (Weak). Benefit ≥ Risk
- Class III: No Benefit (Moderate). Benefit = Risk
- Class III: Harm (Strong). Risk > Benefit

Levels of Evidence (LOE):

- Level A: High-quality evidence from more than one RCT, meta-analyses of high-quality RCTs, one or more RCT corroborated by high-quality registry studies.
- Level B-R (Randomized): Moderate-quality evidence from one or more RCTs, meta-analyses of moderate-quality RCTs.
- Level B-NR (Nonrandomized): Moderate-quality evidence from one or more well-designed nonrandomized studies, observational studies, or registry studies, meta-analyses of such studies.
- Level C-LD (Limited data): Randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, physiological or mechanistic studies in human subjects.
- Level C-EO (Expert opinion): Consensus of expert opinion based on clinical experience.

Data from Reference 16.

Vasopressin

Vasopressin, also known as antidiuretic hormone, is a potent, nonadrenergic vasoconstrictor that increases blood pressure and systemic vascular resistance. Although it acts on various receptors throughout the body, its vasoconstrictive properties are due primarily to its effects on the V_1 receptor. Measurement of vasopressin levels in patients undergoing CPR has shown a high correlation between the levels of endogenous vasopressin released and the potential for ROSC.[50] In one study, plasma vasopressin concentrations were approximately three times as high in survivors compared with nonsurvivors, suggesting that vasopressin is released as an adjunct to epinephrine in life-threatening events such as cardiac arrest.[51]

Vasopressin is proposed to have several advantages over epinephrine. First, the metabolic acidosis that frequently accompanies cardiac arrest can blunt the vasoconstrictive effect of adrenergic agents such as epinephrine. This effect does not occur with vasopressin. Second, the stimulation of beta-receptors caused by epinephrine can increase myocardial oxygen demand and complicate the post-resuscitation phase of CPR. This is not seen with vasopressin use because it does not act on beta-receptors. Vasopressin also may have a beneficial effect on renal blood flow by stimulating V_2 receptors in the kidney, causing vasodilation and increased water reabsorption. With regard to splanchnic blood flow (ie, blood flow to the gastrointestinal tract), however, vasopressin has a detrimental effect when compared to epinephrine.[50] Despite these theoretical advantages with vasopressin, clinical outcomes are not superior to that achieved with epinephrine alone.[52] Furthermore, vasopressin in combination with epinephrine offers no advantage over epinephrine alone.

A multidrug regimen that included vasopressin plus corticosteroid therapy has been evaluated in the setting of in-hospital cardiac arrest.[53-55] The rationale is based on the hemodynamic effects of steroids alone with their potential to impact the intensity of the post-resuscitation systemic inflammatory response and organ dysfunction. A recent meta-analysis observed a favorable effect on ROSC and survival to hospital discharge with good neurologic function using this multidrug regimen.[56] The largest randomized controlled trial to evaluate this multidrug approach combined vasopressin (20 units administered after each dose of epinephrine, maximum cumulative dose of 80 units) plus a single dose of methylprednisolone 40

mg.[55] A significant difference in ROSC was detected in the study group but no difference in 30-day survival or survival with favorable neurologic function was detected. Possible reasons for these disparate results could include the lack of corticosteroid use in the post-resuscitation phase and the time to trial drug administration, which was longer in this trial.

In summary, vasopressin may be considered in cardiac arrest but offers no benefit when used as a substitute for or in combination with epinephrine compared to the standard dose of epinephrine alone.[16] The combination of methylprednisolone, vasopressin, and epinephrine will require further study before this approach could be routinely recommended.

Antiarrhythmics

Amiodarone or lidocaine are suggested in adults with VF/PVT refractory to defibrillation and epinephrine therapy. The purpose of antiarrhythmic drug therapy following unsuccessful defibrillation and vasopressor administration is to prevent the development or recurrence of VF and PVT. However, clinical evidence demonstrating improved survival to hospital discharge is lacking.[57,58]

A large, randomized, double-blind trial in patients with out-of-hospital cardiac arrest secondary to VF or PVT reported a higher incidence of survival to hospital admission but no difference in survival to hospital discharge.[59] This was the first trial to demonstrate the benefit of any antiarrhythmic agent over placebo in patients with out-of-hospital cardiac arrest. A subsequent trial compared amiodarone with lidocaine in patients with out-of-hospital cardiac arrest due to VF.[60] In this trial, amiodarone was associated with improved survival to hospital admission compared with lidocaine but there was no difference in survival to hospital discharge. A most recent trial compared amiodarone and lidocaine to placebo in patients with an out-of-hospital arrest with shock-resistant VF/PVT.[61] Both agents were associated with an increase in survival to hospital admission compared to placebo. However, no significant difference in survival to hospital discharge was observed for amiodarone versus placebo, lidocaine versus placebo, or amiodarone versus lidocaine. A subgroup analysis noted higher rates of survival to hospital discharge with both agents (versus placebo) in patients with bystander-witnessed cardiac arrest.

Magnesium

Severe hypomagnesemia has been associated with VF/PVT, but the routine administration of magnesium during a cardiac arrest has not demonstrated any benefit in clinical outcomes. Two observation trials noted an improvement in ROSC in patients with arrests associated with torsades de pointes.[16] Therefore, magnesium should only be administered in the setting of torsades de pointes.

Thrombolytics

Since most cardiac arrests are related to either myocardial infarction or pulmonary embolism (PE), several investigators have evaluated the role of thrombolytics during CPR. Initial studies evaluating the use of thrombolytics in cardiac arrest yielded mixed results. The most rigorous study performed to date randomized patients with out-of-hospital cardiac arrest to receive either tenecteplase or placebo.[62] Both ROSC and survival to hospital discharge were similar between groups, criteria for futility were met, and the trial was terminated. The incidence of intracranial hemorrhage was significantly greater with tenecteplase versus placebo (2.7% vs 0.4%). Given these results, fibrinolytic therapy should not be used routinely in cardiac arrest. When PE is suspected, its use may be warranted.[16]

Pulseless Electrical Activity and Asystole

Nonpharmacologic Therapy

4 Pulseless electrical activity is defined as the absence of a detectable pulse and the presence of some type of electrical activity other than VF or PVT. Patients with PEA have mechanical cardiac contractions but they are too weak to produce a palpable pulse or blood pressure. Although PEA is classified as a “rhythm of survival,” the likelihood of successful resuscitation is much lower than seen with VF/PVT.[1] PEA is often caused by a treatable underlying cause, and the resuscitation team must quickly identify and correct it if the resuscitation is to be successful (Table 41-2). Asystole occurs when there is a lack of electrical activity in the heart and appears as a flat line on the ECG. Asystole is often not amenable to treatment. Like PEA, successful treatment of asystole depends almost entirely on diagnosing the underlying cause.

TABLE 41-2

Underlying Causes of Pulseless Electrical Activity and Asystole

Condition	Clues	Treatment
Hypovolemia	History, flat neck veins	Intravenous fluids
Hypoxia	Cyanosis, blood gases, airway problems	Ventilation, oxygen
Hydrogen ion (acidosis)	History of bicarbonate-responsive preexisting acidosis	Sodium bicarbonate, hyperventilation
Hyper (Hypo) kalemia	History of renal failure, diabetes, recent dialysis, dialysis fistulas, medications	Calcium chloride, insulin, glucose, sodium bicarbonate, sodium polystyrene sulfonate, dialysis
Hypothermia	History of exposure to cold, central body temperature	Rewarming, oxygen, intravenous fluids
Hypoglycemia	History of diabetes	Glucose infusion
Toxin (Drug overdose)	Bradycardia, history of ingestion, empty bottles at the scene, pupils, neurologic exam	Drug screens, intubation, lavage, activated charcoal
Tamponade (Cardiac)	History (trauma, renal failure, thoracic malignancy), no pulse with CPR, vein distention, impending tamponade-tachycardia, hypotension, low pulse pressure changing to sudden bradycardia as terminal event	Pericardiocentesis
Tension pneumothorax	History (asthma, ventilator, chronic obstructive pulmonary disease, trauma), no pulse with CPR, neck vein distention, tracheal deviation	Needle decompression
Thrombosis, coronary	History, ECG, enzymes	PCI, thrombolytics, oxygen, nitroglycerin, heparin, aspirin, morphine
Thrombosis, pulmonary	History, no pulse with CPR, distended neck veins	Pulmonary arteriogram, surgical embolectomy, thrombolytics
Trauma	History, examination	Volume infusion, intracranial pressure monitoring, bleeding control, surgical intervention

Data from Reference 16.

The algorithm for treating PEA and asystole is the same. Both conditions require CPR, airway control, and IV access. Asystole should be reconfirmed by checking a second lead on the cardiac monitor. Defibrillation should be avoided because the parasympathetic discharge that occurs with defibrillation may reduce the chance of ROSC and worsen the chance of survival. High-quality CPR without interruption remains an emphasis along with identifying a correctable cause.

Pharmacologic Therapy

The primary pharmacologic agent used in the treatment of asystole or PEA is epinephrine. In a systematic review of randomized controlled trials

evaluating epinephrine in out-of-hospital cardiac arrest due to nonshockable rhythms, significant improvements were observed in ROSC, survival to hospital admission, and 3-month survival.[33] Survival with good neurologic function at 3-months improved, albeit not statically significant. Nevertheless, the global benefits of epinephrine were most apparent in patients with nonshockable versus shockable rhythms.

Similar to shockable rhythms, the time to epinephrine administration is an important confounder related to its efficacy. One large study of patients with out-of-hospital cardiac arrest from nonshockable rhythms reported a 4% decrease in the odds of survival to hospital discharge with each minute delay in epinephrine administration.[63] Furthermore, the odds of surviving with good neurologic function decreased by 6% with each minute delay. Other observational studies have yielded similar results. In a large North American registry trial, survival to hospital discharge was highest when epinephrine was administered within 5 minutes after EMS arrival and decreased with each 5-minute period thereafter.[37] A study from a Japanese database revealed worse neurological outcomes when the time to epinephrine administration exceeded 10 minutes.[64] Early epinephrine administration is also important after in-hospital cardiac arrests with nonshockable rhythms. In one large study using the Get with the Guidelines-Resuscitation database, a step-wise decrease in survival was observed with each incremental delay in epinephrine administration.[39] Thus, epinephrine should be administered as soon as possible.

Acid/Base Management

Acidosis seen during cardiac arrest results from decreased blood flow and inadequate ventilation. Chest compressions generate only approximately 25% of normal cardiac output, leading to inadequate organ perfusion, tissue hypoxia, and metabolic acidosis. In addition, the lack of ventilation causes retention of carbon dioxide, leading to respiratory acidosis. Acidosis produces not only reduced myocardial contractility but also lowers the fibrillation threshold. Despite the deleterious effects of acidosis on normal physiology, sodium bicarbonate has not been shown to improve ROSC or survival to hospital discharge.[65] One large observational study reported sodium bicarbonate use was associated with a lower probability of both ROSC and a favorable neurologic outcome.[66] In addition, this negative association persisted in the subgroup of patients having arrests of long duration (defined as >22.6 minutes of resuscitation) conflicting with some beliefs that sodium bicarbonate may be useful in this setting.

Sodium bicarbonate may have detrimental effects because of the following reaction: $[HCO_3^-] + [H^+] \leftrightarrow [H_2O] + [CO_2]$.[67] When sodium bicarbonate is added to an acidic environment, the reaction will shift to the right, thereby increasing tissue and venous hypercarbia. The carbon dioxide generated by this reaction will diffuse into the cell and decrease intracellular pH. The accumulation of intracellular carbon dioxide, specifically within the myocardium, is inversely correlated with CPP produced by CPR. Intracellular acidosis also will decrease myocardial contractility, further complicating the low-flow state associated with CPR. Furthermore, treatment with sodium bicarbonate often overcorrects extracellular pH because sodium bicarbonate has a greater effect when the pH is closer to normal. The induced alkalosis causes an increase in the affinity of oxygen to hemoglobin (“left shift”), thus interfering with oxygen release into the tissues.

Sodium bicarbonate is not recommended for routine use in patients with cardiac arrest.[16] It can be considered in special circumstances such as patients with hyperkalemia, tricyclic antidepressant overdose, or salicylate toxicity.

Postresuscitative Care

5 Following the ROSC from a cardiac arrest, patient management should be directed toward the postcardiac arrest syndrome.[68] There are four main components of the postcardiac arrest syndrome which highlight succinct pathophysiologic processes and potential areas for treatment: hypoxic brain injury, myocardial dysfunction, systemic ischemia-reperfusion response, and the underlying precipitating pathology (Table 41-3).[69] Many of the concepts within these four components surround the principles of basic ICU care (eg, adequate oxygenation, circulatory support, hemodynamic optimization, and prevention of secondary brain injury). Similar to other ICU patients, a systems-based approach should be used to assess the role of drug therapy. Key components of pharmacotherapy related to postcardiac arrest care are described below.

TABLE 41-3

Postcardiac Arrest Syndrome

Syndrome	Pathophysiology	Clinical Manifestation
Hypoxic brain injury	• Impaired cerebrovascular autoregulation • Cerebral edema • Postischemic neurodegeneration	• Seizures • Coma • Myoclonus • Cognitive dysfunction • Cortical/Spinal Stroke • Brain death
Myocardial dysfunction	• Global hypokinesis • Acute coronary syndrome	• Reduced cardiac output • Cardiogenic shock • Dysrhythmias
Systemic ischemia-reperfusion response	• Systemic inflammatory response syndrome • Impaired vasoregulation • Hypercoagulability • Microcirculatory dysfunction • Adrenal suppression • Immunosuppression	• Tissue hypoxia • Hypotension • Fever • Hyperglycemia • Infection • Multi-system organ failure
Underlying precipitating pathology	• Cardiovascular disease • Pulmonary disease • Hypovolemia/Hemorrhage • Stroke • Pulmonary embolism • Poisoning/overdose • Infection • Electrolyte disturbances	• Clinical manifestation will be specific to the underlying cause

Data from Reference 69.

Neurologic Management and Prevention of Secondary Brain Injury

Following the restoration of blood flow after a cardiac arrest, there is a sequence of chemical cascades and destructive enzymatic reactions that result in edema, cerebral hypoxia, and neuronal injury. These reactions include free-radical production, excitatory amino acid release, and calcium shifts, which lead to mitochondrial damage and apoptosis (programmed cell death).[70] In addition, seizures, hyperglycemia, and hyperthermia can increase metabolic demand and further contribute to secondary hypoxic brain injury. The severity of hypoxic brain injury is a key determinant for survival; thus, appropriate preventative or treatment strategies are crucial.

Targeted Temperature Management

Targeted temperature management (TTM) has been a cornerstone of post-resuscitation care for the last 20 years. TTM can protect against cerebral

injury by suppressing the chemical reactions associated with cerebral injury. Additionally, TTM can decrease cerebral metabolism and oxygen consumption. For each 1°C drop in temperature, cerebral metabolism decreases by 6% to 10%.[70]

Early success with TTM was described in two pivotal trials.[71,72] In the first trial, patients who had been resuscitated after cardiac arrest due to VF but remained comatose were assigned randomly to undergo TTM through therapeutic hypothermia, targeting a temperature of 32°C to 34°C (89.6°F to 93.2°F), for 24 hours.[71] More patients in the hypothermia group achieved a favorable neurologic outcome compared to the normothermia group. The second study targeted 33°C (91.4°F) maintained for 12 hours.[72] Likewise, more patients in the hypothermia group had good neurologic function at the time of hospital discharge (to either home or a rehabilitation facility) compared to patients in the normothermia group.

Since the publication of these landmark articles, several randomized controlled trials evaluating TTM have produced mixed results. One randomized controlled trial compared TTM delivered at 33°C versus 36°C (91.4°F vs 96.8°F) for 36 hours to assess whether the benefits of TTM were related to hypothermia or prevention of hyperthermia, which occurred periodically in a previous trial.[73] Overall, this study reported no significant differences in all-cause mortality, end-of-trial mortality, or poor neurologic function. A second randomized controlled trial evaluated the impact of prehospital cooling on survival.[74] Although the target temperature (less than 34°C [89.6°F]) was reached approximately 1 hour sooner in the intervention group compared to controls, prehospital cooling was not associated with increased survival to hospital discharge or improvement in neurological status. Another study found that the duration of TTM (24 hours compared to 48 hours) had no impact on neurologic outcomes assessed at 6 months.[75] In one trial, patients with nonshockable rhythms who achieved ROSC and who were randomized to TTM targeting hypothermia (33°C [91.4°F]) had improved survival with a favorable neurologic outcome at day 90 compared to those who received normothermia (37°C [98.6°F]).[76] The most recent trial (TTM-2 trial) compared hypothermia (33°C [91.4°F]) versus normothermia (37°C [98.6°F]) in patients with both shockable and nonshockable rhythms and found no significant differences in 6-month mortality or poor functional outcome.[77] Similarly, there were no differences based on the initial rhythm being shockable or nonshockable. A subsequent systematic review evaluated the impact of TTM at 32-34°C (89.6-93.2°F) versus normothermia and found no differences in hospital survival, survival to 90 or 180 days, and survival with good neurologic outcome.[78]

One potential reason for these discordant results could be the influence of initial illness severity assessed immediately post-ROSC. One study evaluated survival to hospital discharge in patients who received TTM at 33°C or 36°C (91.4°F or 96.8°F), stratified by illness severity using the Pittsburgh Cardiac Arrest Category (PCAC) score.[79] There was a robust interaction between PCAC score and the effect of TTM at 33°C (91.4°F) whereby a greater benefit was observed in patients with higher severity of illness. In contrast, in patients with lower severity of illness, 36°C (96.8°F) was associated with higher survival rates. Further prospective research will have to validate these findings.

Current guidelines (published before the TTM-2 trial data were available) recommend TTM between 32 and 36°C (89.6°F and 96.8°F) for at least 24 hours.[16] Following the TTM period, fever should be prevented. However, a draft of the Consensus on Science with Treatment Recommendations (CoSTR) for TTM suggests preventing fever by targeting a temperature less than 37.5°C (99.5°F), acknowledging that the benefit of targeting hypothermia (32-34°C [89.6-93.2°F]) in subpopulations surviving cardiac arrest is unknown.[80]

Inducing hypothermia is not without risk. Shivering occurs during the induction phase, increasing metabolic rate and myocardial oxygen demand. Several strategies exist to blunt the thermoregulatory response to hypothermia, and these measures should be implemented accordingly.[81] These measures include acetaminophen, buspirone, magnesium, meperidine, sedation with dexmedetomidine or propofol, and analgesia with fentanyl. In some cases, neuromuscular blocking agents (NMBA) may be required. Neuromuscular blockade, however, may mask the appearance of seizures which are common postcardiac arrest. One randomized study showed no difference in serum lactate levels, survival, or neurologic function with continuous NMBA.[82] In contrast, a large observational study found that as-needed NMBA increased the odds of good outcomes compared to escalating sedation doses without NMBA.[83] When an NMBA is required, as-needed, intermittent dosing regimens are preferred over continuous infusions.

Hypothermia can also affect drug metabolism and clearance resulting in supratherapeutic concentrations.[84] These alterations may persist even upon rewarming into the posttreatment period. This is particularly relevant for sedatives and analgesics, which could confound prognostication. In fact, midazolam clearance is estimated to decrease by up to 11% for each degree Celsius.[84] Propofol clearance is 23% lower in hypothermic compared to normothermic patients. A 45% decrease in clearance has been noted with fentanyl. Careful dose titration should occur to minimize drug accumulation induced by TTM.

Other potential complications described with TTM include coagulopathy, dysrhythmias, bradycardia, diuresis, electrolyte disorders, hyperglycemia, and infections.[81] An intracellular shift of electrolytes like potassium can occur with hypothermia therefore frequent assessment and supplementation are required. Aggressive repletion, however, should be avoided because hyperkalemia may occur during rewarming as sequestered potassium is released from the intracellular compartment.

Seizures

Seizures postcardiac arrest are an indicator of severe brain injury and are associated with poor prognosis. The incidence of seizures is approximately 10% to 30%.[85,86] Seizures usually occur within 8 to 24 hours postarrest but can occur later, especially after rewarming in patients treated with TTM. Continuous electroencephalogram monitoring for at least 72 hours is suggested. Either valproic acid or levetiracetam should be used as first-line therapy for the treatment of seizures. Medications for prophylaxis of seizures are not indicated.

Respiratory Management

After ROSC, it is imperative to ensure a secure airway is in place (ie, an endotracheal tube) and oxygenation is appropriate. Rearrest is common in the first minutes after resuscitation (occurring in roughly one of five cases). Hypoxia and hypotension are also frequently seen.[81] Both hypoxia and hyperoxia are associated with adverse outcomes after cardiac arrest and should be avoided.[81] Initially, 100% oxygen should be used during the resuscitation effort. If ROSC is obtained, the fraction of inspired oxygen can be titrated down as tolerated to maintain an oxygen saturation of 92-98% (0.92-0.98).[16] Overventilation, which leads to hypocapnia, should be avoided since hypocapnia causes vasoconstriction and may lead to cerebral ischemia.

Cardiovascular and Hemodynamic Management

Given that cardiac ischemia is the most common cause of cardiac arrest, a rapid search for ECG changes consistent with acute myocardial infarction should be undertaken immediately.[81] If an acute myocardial infarction is present, urgent revascularization should be performed.

Shock will be present in 50% to 70% of patients post-ROSC.[87] Cardiac echocardiography should be performed to evaluate myocardial dysfunction and can guide pharmacotherapy decisions. Volume management should be individualized for each patient based on underlying organ dysfunction, the hemodynamic target chosen, and the etiology of the arrest. Inotropes and vasopressors should be used accordingly. Steroids should not be routinely given but can be considered in refractory cases or when adrenal insufficiency is evident.

The choice for a target blood pressure is a balance between overall heart function (eg, presence of left ventricular dysfunction) and the need to maintain adequate cerebral perfusion. This is complicated by the fact that following ROSC, cerebral hypoperfusion is common, lasting several hours to days after resuscitation. During this time, cerebral vascular resistance is increased and autoregulation is impaired. Autoregulation is the ability of the cerebral vasculature to regulate constant blood flow to the brain across a range of systemic blood pressures. In the post-resuscitation phase, increased systemic pressures are needed to maintain adequate blood flow to the brain. While an optimal goal of mean arterial pressure (MAP) target has not been determined, augmenting blood pressure to achieve a goal of MAP of more than 80 mm Hg has been recommended, especially when advanced cerebral monitoring is not in use.[81]

Glucose Management

Both hyperglycemia and hypoglycemia are associated with poor outcomes in critically ill patients. Hyperglycemia is particularly common postcardiac arrest and can be influenced by TTM.[88] During therapeutic hypothermia, insulin sensitivity is significantly lower and highly variable. Upon rewarming, insulin sensitivity increases which could increase the risk for hypoglycemia. One small study compared strict (72-108 mg/dL [4-6 mmol/L]) with moderate (108-144 mg/dL [6-8 mmol/L]) glycemic control in patients with ROSC after out-of-hospital cardiac arrest.[89] There was no survival benefit recognized with strict glucose control but hypoglycemic events were higher. Maintaining glucose between 81 and 180 mg/dL (4.5 and 10 mmol/L) after cardiac arrest is suggested.

Infectious Disease Management

Therapeutic hypothermia is associated with an increased risk for infectious complications, particularly ventilator-associated pneumonia. A large trial evaluated the benefit of a short course (48 hours) of antibiotic therapy (amoxicillin-clavulanate) in patients who received TTM at 32-34°C (89.6-93.2°F).[90] Patients who received antibiotic prophylaxis had a lower incidence of early-onset pneumonia but no differences were observed in the incidence of late-onset pneumonia, number of ventilator-free days, ICU length of stay, or mortality. Routine use of antibiotic prophylaxis, therefore, is not recommended.[18]

Special Populations

Asthma

Asthma is a common disorder, and despite modern therapies, there are still in excess of 3,500 asthma-related deaths annually in the United States.[16] True cardiac arrest in asthma is infrequent, as the primary pathophysiology is respiratory compromise and poor ventilation.[91] Asthma exacerbations are a combination of bronchoconstriction, airway inflammation, and mucous plugging. This leads to severe air trapping, hyperinflation, and hemodynamic compromise. While wheezing is common in an asthma exacerbation, it does not correlate with the degree of airway obstruction. In contrast, with worsening disease (and subsequent decrease in airflow), wheezing may disappear. Further, several disease states cause wheezing, including pulmonary edema, pneumonia, anaphylaxis, foreign bodies, and tumors.

Patients with life-threatening asthma need to be treated aggressively with bronchodilators and corticosteroids. Adjunctive therapies include anticholinergics, magnesium sulfate, ketamine, helium/oxygen mixtures, or inhaled anesthetics.[92-96] Noninvasive ventilation can be attempted if the patient is deteriorating and still awake. This may prevent the need for mechanical ventilation.[97] The decision to intubate is a clinical judgment. However, the endotracheal tube will not solve the airway problem and aggressive asthma management needs to continue after intubation. In addition, intubation and positive airway pressure can trigger further bronchoconstriction or hemodynamic compromise.

The provision of BLS and standard ACLS measures should be followed in patients with acute asthma.[16] However, since the effect of auto-positive end-expiratory pressure, known as breath stacking, can be severe, a strategy of low respiratory rate and volume ventilation may be appropriate.[16] Similarly, for cardiac arrest in patients with acute asthma, especially when ventilation is difficult, tension pneumothorax should be strongly considered.[16]

Anaphylaxis

Anaphylaxis is a severe allergic reaction that can lead to airway obstruction and cardiovascular collapse. In the United States, at least 1.6% of adults have experienced anaphylaxis with about 200 individuals dying each year.[16] The initial signs can be nonspecific, but a “sense of impending doom” is common. Rhinitis often leads to laryngeal edema with stridor in the upper airway. Bronchoconstriction often mimics an acute asthma attack.

Cardiovascular collapse is common in severe anaphylaxis due to vasodilation and increased capillary permeability. This can rapidly lead to myocardial hypoperfusion and ischemia and to full cardiac arrest. There are no randomized trials comparing strategies to manage arrest due to anaphylaxis.[16] Therefore, standard basic and advanced life support measures should be followed.

Clinicians are advised to stop any drug or remove any trigger (eg, stinger after a bee sting) suspected of causing anaphylaxis. Early advanced airway management is recommended due to the potential for rapidly developing laryngeal edema. Epinephrine remains the cornerstone of the treatment.[16] The recommended dose is 0.2 to 0.5 mg and should be administered via intramuscular injection to all patients with signs of systemic allergy.[16] This can be repeated every 5 to 15 minutes if there is no clinical improvement. About 10% of patients will require more than one dose and 98% will respond with two or three doses.[98] Fluid resuscitation is usually required for restoration of circulation and is supported by one study in which the combination of fluid resuscitation and epinephrine was effective in treating hypotension unresponsive to vasoactive drugs.[99] Other agents such as antihistamines, inhaled beta-agonists, and IV corticosteroids have been used successfully in anaphylaxis and may be considered in cardiac arrest due to anaphylaxis but there are no data illustrating their benefit.[16]

Opioid Overdose

Opioid-associated cardiac arrests are responsible for approximately 115 deaths per day in the United States, largely affecting individuals aged 25 to 65

years.[16] Opioid overdose is characterized by central nervous system and respiratory depression that ultimately progresses to respiratory arrest and then cardiac arrest. Maintaining an airway and ventilation are, therefore, the highest priorities. Naloxone is an effective antidote to reverse the effect of opioids, but there are no studies demonstrating improvements in outcomes during cardiac arrest.[16] Naloxone should be administered along with standard basic and advanced life support measures but should not delay components of high-quality CPR. Repeat doses may be necessary with ingestion of long-acting or sustained release opioids. Naloxone is ineffective for arrests caused by nonopioids or other overdose scenarios.

Pregnancy

Pregnancy is a unique situation where the survival of both the fetus and the mother depends on CPR. Despite the fact that pregnant patients are younger than most cardiac arrest victims, the incidence of cardiac arrest during pregnancy appears to be on the rise in the United States.[16] Historically, survival has been poor but survival rates of nearly 60% have been reported.[100] Survival is largely dependent on the underlying etiology. The most common causes of cardiac arrest during pregnancy are anesthetic complications, accidents, bleeding, cardiovascular, drugs, embolism, fever, and hypertension.[101]

The best hope for survival of the fetus is maternal survival. Fetal monitoring is not advised during cardiac arrest because of potential interference with maternal resuscitation. High-quality chest compressions are essential and hand placement is similar to a nonpregnant patient. Because the vena cava and aorta can be obstructed by the uterus in the second and third trimesters during pregnancy, CPR procedures should be modified. Manual lateral uterine displacement (ie, pulling the uterus to the side) is recommended.[16] Alternatively, tilting the patient laterally by approximately 30 degrees can be used but the quality of chest compressions is compromised.

Pregnant patients are more prone to hypoxia; thus, oxygenation and airway management are important. The airway may be smaller because of the hormonal changes and edema.[101] Similarly, because of increased intra-abdominal pressure exerted by the uterus, as well as hormonal changes that change the resting state of the gastroesophageal sphincter, there is an increased risk of aspiration. The rescuer may need to give smaller respiration volumes than normal.

The ACLS provider should follow the standard guidelines for the pregnant patient, including the same use of chest compressions, defibrillation, and medications.[101] Epinephrine remains the vasopressor of first choice despite concerns that it can diminish uterine blood flow. Antiarrhythmics should be considered for refractory, shock-resistant VF/PVT. No medication should be withheld in the setting of cardiac arrest because of concerns about fetal teratogenicity. While there are clear changes in pharmacokinetic parameters (ie, the volume of distribution and clearance) during pregnancy, there are limited data to justify alternative dosing strategies. Standard doses, therefore, are recommended.

Although the etiology of arrest in pregnancy is often the same as in the nonpregnant patient, there are several unique causes that need to be considered.[101] Excess magnesium sulfate administration (ie, iatrogenic from treating eclampsia) can prompt cardiac arrest. In such cases, the therapeutic administration of calcium can be lifesaving. An amniotic embolism can lead to complete cardiovascular collapse during labor and delivery. Pre-eclampsia/eclampsia developing after the 20th week of gestation can produce hypertension and multiple organ dysfunction, including cardiac arrest. Vascular events including acute coronary syndromes and acute PE can also be a cause.

It is paramount to remember that unless circulation is restored to the mother, both the mother and the fetus will succumb. The resuscitation leader should consider the need for emergent cesarean delivery if ROSC is not obtained within 5 minutes.[16] In patients who achieve ROSC but remain comatose, TTM with fetal monitoring is recommended.

Accidental Hypothermia

Accidental (unintentional) hypothermia (not therapeutic hypothermia used postarrest) occurs when the body temperature is less than 30°C (86°F). It is associated with marked derangements in body function. Because it can depress virtually every body system, including pulse and respiration, the patient may appear to be dead. If the patient still has a perfusing rhythm, therapy is directed toward rewarming techniques. For mild hypothermia (ie, >34°C [93.2°F]), passive rewarming is recommended.[102] For moderate hypothermia (ie, 30°C–34°C [86°F–93.2°F]), active external rewarming is recommended, and for severe hypothermia (ie, <30°C [86°F]), active internal rewarming is recommended. Patients need to be manipulated very gently as VF is sometimes precipitated by movement.

If the patient is in cardiac arrest, then the standard BLS algorithm should be followed. Pulse and respiratory rates may be slow or difficult to detect and ECG may show asystole. If the victim displays no signs of life, then chest compressions and rescue breaths should ensue immediately. If the patient is in VF or PVT, electrical therapy should be given in a standard manner and CPR should immediately resume. Source of heat loss should be minimized (ie, removal of wet clothing, protection from the environment). The role for medications is unclear. Some resources recommended withholding epinephrine when the body temperature is less than 30°C (86°F). Current recommendations state it is reasonable to administer epinephrine according to standard ACLS practices.[16]

It is debatable when to stop resuscitative efforts in hypothermic patients. Many authors have proposed that a patient should not be pronounced dead until the core temperature has been restored to near normal.[102]

Trauma

Cardiac resuscitation of the trauma arrest patient should follow standard BLS and ACLS practices. Survival rates following an out-of-hospital cardiac arrest due to trauma are low.[98] Survival is higher in young patients with treatable penetrating injuries. Common reversible causes of traumatic cardiac arrest are hemorrhage, tension pneumothorax, asphyxia, and pericardial tamponade.

Trauma patients often suffer head or cervical injuries; thus, cervical spine precautions should be used. A jaw thrust maneuver is the preferred way to open the airway, with in-line stabilization during attempts at advanced airway placement.[16] Inadequate ventilation of one side is usually due to tube malposition, tension pneumothorax, or hemothorax. These conditions are usually treated by medical personnel at the hospital after transport.

Chest compressions should be performed in a standard manner. Chest compressions are less likely to be effective when cardiac arrest is due to hypovolemia, cardiac tamponade, or tension pneumothorax. Treatment for these “reversible causes” should be prioritized.

Ongoing hemorrhage must be controlled with either temporizing or definitive measures. Restoration of blood volume with blood products is essential as resuscitation is unlikely if the patient has severe hypovolemia. Tranexamic acid can be considered for patients with traumatic hemorrhage who present within 3 hours from injury.[103] Resuscitative endovascular balloon occlusion of the aorta is being evaluated in both traumatic and nontraumatic cardiac arrest to improve the effectiveness of chest compressions. Available data suggest this technique may be beneficial.[104]

Open thoracotomy for trauma-induced arrest may be indicated for select patients.[105] Open thoracotomy can allow relief of tamponade, control of major vessel hemorrhage, or direct repair. Open thoracotomy is a strong recommendation for patients who are pulseless but have signs of life after penetrating thoracic injury.[105] In the setting of penetrating extra-thoracic injury or blunt injury, open thoracotomy is a conditional recommendation.

A unique cause of cardiac arrest caused by a blow to the anterior chest or sternum during the repolarization part of the cardiac cycle is called “Commotio Cordis.”[106] These events are commonly seen in young athletes and can be caused by a fall or a baseball or hockey puck striking the sternum. Prompt recognition and rapid defibrillation are often lifesaving. Provision of BLS, the use of an AED, and standard ACLS procedures are appropriate for this type of arrest.

Drowning

Drowning is the result of primary respiratory impairment following immersion/submersion in a liquid. It is a common, preventable cause of morbidity and mortality. Cardiac arrest in this setting is due to hypoxia. The most powerful predictor of outcome, therefore, is the duration of submersion. In one study, the probability of a good outcome was only 2% when the submersion duration exceeded 10 minutes.[107] With submersion durations that exceed 25 minutes, resuscitation efforts may be futile.

Because hypoxia is the underlying etiology of cardiac arrest in drowning victims, the traditional A-B-C approach should be used instead of C-A-B.[102] Early care consists of immediate rescue breathing, even before they are removed from the water. Once the victim is removed from the water, immediate chest compressions should be started if they are pulseless. Drowning victims can present with any of the pulseless rhythms; standard guidelines for these rhythms should be followed. A “Drowning Chain of Survival” has been proposed to improve outcomes.[108] The five links in the chain are as follows: prevent drowning, recognize distress, provide flotation, remove from water, and provide care as needed.

Electrocution/Lightning

There are many etiologies of electrical shock injuries including a lightning strike, high-tension current, or household current. The severity of injury depends on the site, type of current, duration of contact, pathway, and the magnitude of delivered electricity.

Cardiac arrest is common in electrical injury due to the current passing through the heart during the "vulnerable period" of the cardiac cycle. In large-current events, such as lightning strikes, the heart undergoes massive depolarization. In some cases, the intrinsic pacemaker can restore an organized cardiac electrical cycle. Injury to other muscles, however, particularly the thoracic musculature, and suppression of the respiratory center can lead to inadequate ventilation, hypoxia, and subsequent cardiac arrest. Ventilatory support, therefore, must be maintained after ROSC is achieved.

When approaching a victim of electrocution, the rescuer must first be certain of his or her own safety. Prompt CPR and ACLS, when available, is indicated. Electric shock is often associated with multiple trauma, including spinal injury, multiple injuries to the skeletal muscles, as well as fractures. These factors need to be evaluated by the resuscitation team.

Airway control may be difficult due to the edema that often accompanies electrical injuries; thus, an advanced airway early in the treatment process is recommended.[102] With soft tissue swelling, there is often a need for aggressive fluid resuscitation in these patients. The underlying tissue, or visceral organ damage, is often worse than the external appearance. It is usually recommended that these patients can be transferred to centers with expertise in dealing with these types of injuries.

Drug Administration

The routes of administration available for drug delivery during CPR include IV (both central and peripheral access), IO, and endotracheal. Each route represents a compromise between access and efficacy in introducing the drug into the central circulation. When selecting a route for drug administration, it is important to minimize any interruptions in chest compressions during CPR.

The traditional access site for parenteral medication administration during a cardiac arrest is a peripheral IV line. Peripheral drug administration yields a peak concentration in the major systemic arteries in roughly 1.5 to 3 minutes but this time can be shortened by up to 40% if the drug is followed by a 20-mL fluid bolus and elevating the extremity.[109] Central venous access will result in a faster and higher peak drug concentration than peripheral access but central line access is not needed in most resuscitation attempts. If a central line is already present, it should be the access site of choice. An appropriately trained provider may consider placing a central line if one is not present and attempts to establish IV or IO access are unsuccessful, but CPR should not be interrupted. Central lines located above the diaphragm are preferable to those located below the diaphragm because of poor blood flow during CPR.

6 If IV access cannot be obtained, IO is the next preferred route for drug and fluid administration.[16] Several IO access devices are commercially available that allow for rapid insertion and are easy to use. Pharmacokinetic data have demonstrated similar areas under the curve and times to peak concentration for sternal IO and central IV administration.[110] Clinical data, however, have suggested outcomes may be worse with IO administration versus IV.[18] IO administration should only be used if initial attempts at IV access are unsuccessful. Potential anatomic sites for insertion of an IO needle are the sternum, tibia, and humerus.[110] The need for cessation of chest compressions, however, along with the risk of injury to the heart or great vessels makes the sternum a less desirable site for insertion. As such, the proximal tibia is typically preferred because it is easy to locate, provides a flat, wide surface for insertion, has minimal subcutaneous layers overlying the bone, and does not interfere with CPR.

If neither IV nor IO access can be established, a few drugs can be administered through an endotracheal tube. These drugs are atropine, lidocaine, epinephrine, naloxone, and vasopressin.[109] There are no data with amiodarone. Medications administered through the endotracheal route will have both a lower and delayed peak concentration than when drugs are administered by the IV or IO routes. In one clinical trial, lower rates of ROSC, hospital admission, and hospital discharge were observed with endotracheal drug administration compared to IV.[109] If the endotracheal route is to be used, the recommended medication dose is 2 to 2.5 times larger than the IV/IO dose. Providers should dilute the medication in 5 to 10 mL of either sterile water or normal saline. Better drug absorption may be achieved with sterile water.[109]

EVALUATION OF THERAPEUTIC OUTCOMES

The optimal outcome following CPR is an awake, responsive, spontaneously breathing patient. Patients must remain neurologically intact with minimal morbidity following the resuscitation if it is to be considered a success.

Monitoring during cardiac arrest includes both CPR performance and physiologic. CPR performance can be assessed using devices that provide real-time feedback on CPR quality. In many cases, rhythm assessment via ECG and pulse checks are the only physiologic parameters available to guide therapy. Palpating a pulse to determine the efficacy of blood flow during CPR, however, has not been shown to be useful. Invasive hemodynamic monitoring (eg, CPP, central venous oxygenation) can provide useful information during CPR but these are seldom available. Arterial diastolic pressure may be a reasonable surrogate for CPP; values less than 20 mm Hg are generally considered suboptimal, and a goal of more than 25 mm Hg is suggested.[111] An arterial central venous oxygen saturation of less than 30% (0.30) is indicative of poor CPR quality.[109]

$ETCO_2$ monitoring is a useful method to assess cardiac output during CPR and has been associated with ROSC. The main determinant of carbon dioxide excretion is the rate of delivery from the peripheral tissues to the lungs. Increasing cardiac output through effective CPR will yield higher $ETCO_2$ levels. Therefore, $ETCO_2$ levels reflect the cardiac output generated by CPR. Persistently low $ETCO_2$ values (<10 mm Hg [1.3 kPa]) during CPR in intubated patients suggest ROSC is unlikely.[16] $ETCO_2$ levels that exceed 20 mm Hg (2.7 kPa) may be associated with a higher chance for ROSC.[18]

Evaluation of outcomes in the post-resuscitation phase should be directed toward the components of the postcardiac arrest syndrome. Because the postcardiac arrest syndrome can affect practically every organ system, a review-of-systems approach for assessment (ie, “head-to-toe”) is strongly suggested. Neuroprognostication should occur at least 5 days after ROSC (or 72 hours after normothermia) for patients who receive TTM because of the prolonged effects of sedatives noted with hypothermia.

The latest link added to the “chain of survival” is recovery. Many patients who survive cardiac arrest suffer from prolonged emotional, cognitive, physical, and neurologic symptoms. In fact, one-third of survivors experience symptoms of anxiety, depression, and posttraumatic stress disorder.[16] Family members and caregivers may also experience stress during the recovery period. A multimodal plan should be provided at hospital discharge that includes instructions for treatment, rehabilitation, and surveillance. In addition, both short-term and long-term expectations should be clearly defined with appropriate action plans for each phase of the recovery.

CONCLUSION

Cardiac arrest is often fatal, but rapid recognition and treatment can result in a favorable outcome. The “Chains of Survival” as described by the AHA provides a framework for treatment. Early recognition and response including high-quality chest compressions with minimal interruptions, early defibrillation, and post-resuscitation care remain major hallmarks of therapy. Nevertheless, there are many areas of uncertainty including the optimal approach for oxygenation and ventilation, the role of drug therapy (eg, epinephrine), the value of TTM, resuscitation targets, and the role of extracorporeal therapies (ie, cardiopulmonary bypass), and the value of neuroprotective agents.[112] A comprehensive research approach, consisting of randomized controlled trials, registry-based studies, pragmatic trials, and animal/laboratory research will be necessary to advance our understanding and improve outcomes.

ABBREVIATIONS

ACLS	advanced cardiac life support
AED	automated external defibrillator
AHA	American Heart Association
BLS	basic life support
CI	confidence interval
CPP	coronary perfusion pressure
CPR	cardiopulmonary resuscitation
ECC	emergency cardiovascular care
ECG	electrocardiogram
EMS	emergency medical services
$ETCO_2$	end-tidal carbon dioxide
IO	intraosseous
IV	intravenous
MAP	mean arterial pressure
OR	odds ratio
PCI	percutaneous coronary intervention
PEA	pulseless electrical activity
PE	pulmonary embolism
ROSC	return of spontaneous circulation
PVT	pulseless ventricular tachycardia
SBP	systolic blood pressure
VF	ventricular fibrillation

REFERENCES

1. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update: A report from the American Heart Association. *Circulation*. 2021;143(8):e254–e743. 10.1161/CIR.0000000000000950

[PubMed: 33501848] .

2. Chan PS, McNally B, Tang F, et al. Recent trends in survival from out-of-hospital cardiac arrest in the United States. *Circulation*. 2014;130:1876–1882. [PubMed: 25399396]

3. Cardiac Arrest Registry to Enhance Survival (CARES) 2020 Annual Report. https://mycares.net/sitepages/uploads/2021/2020_flipbook/index.html?page=1. 2020. Accessed 11/26/2021.

4. Patil KD, Halperin HR, Becker LB. Cardiac arrest: Resuscitation and reperfusion. *Circ Res.* 2015;116(12):2041–2049. 10.1161/CIRCRESAHA.116.304495 [PubMed: 26044255] .

5. Girotra S, Nallamothu BK, Spertus JA, et al. Trends in survival after in-hospital cardiac arrest. *N Engl J Med.* 2012;367(20):1912–20. 10.1056/NEJMoa1109148 [PubMed: 23150959] .

6. Berg RA, Nadkarni VM, Clark AE, et al. Incidence and outcomes of cardiopulmonary resuscitation in PICUs. *Crit Care Med.* 2016;44:798–808. [PubMed: 26646466]

7. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. *Circ Res.* 2015;116:1887–1906. [PubMed: 26044246]

8. Topjian AA, Raymond TT, Atkins D, et al. Part 4: Pediatric basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142(16_suppl_2):S469–S523. 10.1161/CIR.0000000000000901 [PubMed: 33081526] .

9. Ewy GA. Cardiocerebral and cardiopulmonary resuscitation—2017 update. *Acute Med Surg.* 2017;4:227–234. [PubMed: 29123868]

10. Mancini ME, Diekema DS, Hoadley TA, et al. Part 3: Ethical issues: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S383–S396. [PubMed: 26472991]

11. Cooper JA, Cooper JD, Cooper JM. Cardiopulmonary resuscitation: History, current practice, and future direction. *Circulation*. 2006;114:2839–2849. [PubMed: 17179033]

12. Merchant RM, Topjian AA, Panchal AR, et al. Part 1: Executive summary: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142(16_suppl_2):S337–S357. 10.1161/CIR.0000000000000918 [PubMed: 33081530] .

13. Harris AW, Kudenchuk PJ. Cardiopulmonary resuscitation: The science behind the hands. *Heart*. 2018.;104:1056–1061. [PubMed: 29353251]

14. Soar J, Edelson DP, Perkins GD. Delivering high-quality cardiopulmonary resuscitation in-hospital. *Curr Opin Crit Care*. 2011;17:225–230. [PubMed: 21478746]

15. Goharani R, Vahedian-Azimi A, Farzanegan B, et al. Real-time compression feedback for patients with in-hospital cardiac arrest: A multi-center randomized controlled clinical trial. *J Intensive Care*. 2019;7:5–5. 10.1186/s40560-019-0357-5 [PubMed: 30693086] .

16. Panchal AR, Bartos JA, Cabañas JG, et al. Part 3: Adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142(16_suppl_2):S366–S468. 10.1161/CIR.0000000000000916 [PubMed: 33081529] .

17. Andersen LW, Holmberg MJ, Berg KM, et al. In-hospital cardiac arrest: A review. *JAMA.* 2019;321(12):1200–1210. 10.1001/jama.2019.1696

[PubMed: 30912843] .

18. Berg KM, Soar J, Andersen LW, et al. Adult advanced life support: 2020 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2020;142(16_suppl_1):S92–S139. 10.1161/CIR.0000000000000893
[PubMed: 33084390] .

19. Ewy GA. Cardiocerebral and cardiopulmonary resuscitation—2017 update. *Acute Med Surg.* 2017;4(3):227–234. 10.1002/ams2.281
[PubMed: 29123868] .

20. Christenson J, Andrusiek D, Everson-Stewart S, et al. Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. *Circulation*. 2009;120(13):1241–1247. 10.1161/CIRCULATIONAHA.109.852202
[PubMed: 19752324] .

21. Bobrow BJ, Spaite DW, Berg RA, et al. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA.* 2010;304(13):1447–1454. 10.1001/jama.2010.1392
[PubMed: 20924010] .

22. Olasveengen TM, Mancini ME, Perkins GD, et al. Adult basic life support: 2020 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2020;142(16_suppl_1):S41–S91. 10.1161/CIR.0000000000000892
[PubMed: 33084391] .

23. Sutton RM, French B, Meaney PA, et al. Physiologic monitoring of CPR quality during adult cardiac arrest: A propensity-matched cohort study. *Resuscitation*. 2016;106:76–82. 10.1016/j.resuscitation.2016.06.018
[PubMed: 27350369] .

24. Link MS, Atkins DL, Passman RS, et al. Part 6: electrical therapies: Automated external defibrillators, defibrillation, cardioversion, and pacing: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S706–S719.
[PubMed: 20956222]

25. Böttiger BW, Becker LB, Kern KB, et al. BIG FIVE strategies for survival following out-of-hospital cardiac arrest. *Eur J Anaesthesiol.* 2020;37(11):955–958. 10.1097/EJA.0000000000001247
[PubMed: 32467418] .

26. Girotra S, van Diepen S, Nallamothu BK, et al. Regional variation in out-of-hospital cardiac arrest survival in the United States. *Circulation*. 2016;133(22):2159–2168. 10.1161/CIRCULATIONAHA.115.018175
[PubMed: 27081119] .

27. Bækgaard JS, Viereck S, Møller TP, et al. The effects of public access defibrillation on survival after out-of-hospital cardiac arrest: A systematic review of observational studies. *Circulation*. 2017;136(10):954–965. 10.1161/CIRCULATIONAHA.117.029067
[PubMed: 28687709] .

28. Robinson LA, Brown CG, Jenkins J, et al. The effect of norepinephrine versus epinephrine on myocardial hemodynamics during CPR. *Ann Emerg Med.* 1989;18:336–340. [PubMed: 2705665]

29. Paradis NA, Martin GB, Rivers EP, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA.* 1990;263:1106–1113. [PubMed: 2386557]

30. Reynolds JC, Salcido DD, Menegazzi JJ. Conceptual models of coronary perfusion pressure and their relationship to defibrillation success in a porcine model of prolonged out-of-hospital cardiac arrest. *Resuscitation*. 2012;83:900–906. [PubMed: 22266069]

31. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med.* 2018;379(8):711–721. 10.1056/NEJMoa1806842
[PubMed: 30021076] .

32. Jacobs IG, Finn JC, Jelinek GA, et al. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. *Resuscitation*. 2011;82(9):1138–1143. 10.1016/j.resuscitation.2011.06.029
[PubMed: 21745533] .

33. Perkins GD, Kenna C, Ji C, et al. The effects of adrenaline in out of hospital cardiac arrest with shockable and non-shockable rhythms: Findings from the PACA and PARAMEDIC-2 randomised controlled trials. *Resuscitation*. 2019;140:55–63. 10.1016/j.resuscitation.2019.05.007
[PubMed: 31116964] .

34. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA.* 2012;307:1161–1168. [PubMed: 22436956]

35. Nakahara S, Tomio J, Takahashi H, et al. Evaluation of pre-hospital administration of adrenaline (epinephrine) by emergency medical services for patients with out of hospital cardiac arrest in Japan: Controlled propensity matched retrospective cohort study. *BMJ.* 2013;347:f6829. [PubMed: 24326886]

36. Perkins GD, Kenna C, Ji C, et al. The influence of time to adrenaline administration in the Paramedic 2 randomised controlled trial. *Intensive Care Med.* 2020;46(3):426–436. 10.1007/s00134-019-05836-2
[PubMed: 31912202] .

37. Okubo M, Komukai S, Callaway CW, et al. Association of timing of epinephrine administration with outcomes in adults with out-of-hospital cardiac arrest. *JAMA Netw Open*. 2021;4(8):e2120176–e2120176. 10.1001/jamanetworkopen.2021.20176
[PubMed: 34374770] .

38. Andersen LW, Berg KM, Saindon BZ, et al. Time to epinephrine and survival after pediatric in-hospital cardiac arrest. *JAMA.* 2015;314:802–810. [PubMed: 26305650]

39. Donnino MW, Salciccioli JD, Howell MD, et al. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: Retrospective analysis of large in-hospital data registry. *Br Med J.* 2014;348:g3028.

40. Ewy GA, Bobrow BJ, Chikani V, et al. The time dependent association of adrenaline administration and survival from out-of-hospital cardiac arrest. *Resuscitation*. 2015;96:180–185. [PubMed: 26307453]

41. Koscik C, Pinawin A, McGovern H, et al. Rapid epinephrine administration improves early outcomes in out-of-hospital cardiac arrest. *Resuscitation*. 2013;84:915–920. [PubMed: 23523823]

42. Dumas F, Bougouin W, Geri G, et al. Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? *J Am Coll Cardiol.* 2014;64:2360–2367. [PubMed: 25465423]

43. Ristagno G, Tang W, Huang L, et al. Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation. *Crit Care Med.* 2009;37:1408–1415. [PubMed: 19242339]

44. Deakin CD, Yang J, Nguyen R, et al. Effects of epinephrine on cerebral oxygenation during cardiopulmonary resuscitation: A prospective cohort study. *Resuscitation*. 2016;109:138–144. [PubMed: 27592156]

45. Rivers EP, Wortsman J, Rady MY, Blake HC, McGeorge FT, Buderer NM. The effect of the total cumulative epinephrine dose administered during human CPR on hemodynamic, oxygen transport, and utilization variables in the postresuscitation period. *Chest*. 1994;106:1499–1507. [PubMed: 7956410]

46. Larabee TM, Liu KY, Campbell JA, Little CM. Vasopressors in cardiac arrest: A systematic review. *Resuscitation*. 2012;83:932–939. [PubMed: 22425731]

47. Callaham M, Madsen CD, Barton CW, Saunders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. *JAMA.* 1992;268:2667–2672. [PubMed: 1433686]

48. Lindner KH, Ahnefeld FW, Grunert A. Epinephrine versus norepinephrine in prehospital ventricular fibrillation. *Am J Cardiol.* 1991;67:427–428. [PubMed: 1994668]

49. Redding JS, Pearson JW. Evaluation of drugs for cardiac resuscitation. *Anesthesiology*. 1963;24:203–207. [PubMed: 13973493]

50. Wenze IV, Raab H, Dunser MW. Role of arginine vasopressin in the setting of cardiopulmonary resuscitation. *Best Pract Res Clin Anaesthesiol.* 2008;22:287–297. [PubMed: 18683475]

51. Lindner KH, Haak T, Keller A, Bothner U, Lurie KG. Release of endogenous vasopressors during and after cardiopulmonary resuscitation. *Heart*. 1996;75:145–150. [PubMed: 8673752]

52. Holmberg MJ, Issa MS, Moskowitz A, et al. Vasopressors during adult cardiac arrest: A systematic review and meta-analysis. *Resuscitation*. 2019;139:106–121. 10.1016/j.resuscitation.2019.04.008
[PubMed: 30980877] .

53. Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: A randomized clinical trial. *JAMA.* 2013;310:270–279. [PubMed: 23860985]

54. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med.* 2009;169:15–24. [PubMed: 19139319]

55. Andersen Lars W, Isbye Dan, Kjærgaard Jesper, et al. Effect of vasopressin and methylprednisolone vs placebo on return of spontaneous circulation in patients with in-hospital cardiac arrest. *JAMA.* 2021;326:1586. 10.1001/jama.2021.16628.

56. Shah K, Mitra AR. Use of corticosteroids in cardiac arrest: A systematic review and meta-analysis. *Crit Care Med.* 2021;49(6):e642–e650. 10.1097/CCM.0000000000004941
[PubMed: 33729721] .

57. Huang Y, He Q, Yang M, Zhan L. Antiarrhythmia drugs for cardiac arrest: A systemic review and meta-analysis. *Crit Care*. 2013;17:R173. [PubMed: 23938138]

58. Ong ME, Pellis T, Link MS. The use of antiarrhythmic drugs for adult cardiac arrest: A systematic review. *Resuscitation*. 2011;82:665–670. [PubMed: 21444143]

59. Kudenchuk PJ, Cobb LA, Copass MK. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med.* 1999;341:871–878. [PubMed: 10486418]

60. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med.* 2002;346:884–890. [PubMed: 11907287]

61. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med.* 2016;374:1711–1722. [PubMed: 27043165]

62. Bottiger BW, Arntz HR, Chamberlain DA, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med.* 2008;359:2651–

2662. [PubMed: 19092151]

63. Hansen M, Schmicker RH, Newgard CD, et al. Time to epinephrine administration and survival from nonshockable out-of-hospital cardiac arrest among children and adults. *Circulation*. 2018;137(19):2032–2040. 10.1161/CIRCULATIONAHA.117.033067 [PubMed: 29511001] .

64. Goto Y, Maeda T, Goto Y. Effects of prehospital epinephrine during out-of-hospital cardiac arrest with initial non-shockable rhythm: An observational cohort study. *Crit Care*. 2013;17(5):R188–R188. 10.1186/cc12872 [PubMed: 24004456] .

65. Alshahrani MS, Aldandan HW. Use of sodium bicarbonate in out-of-hospital cardiac arrest: A systematic review and meta-analysis. *Int J Emerg Med.* 2021;14(1):21–21. 10.1186/s12245-021-00344-x [PubMed: 33849429] .

66. Kawano T, Grunau B, Scheuermeyer FX. Prehospital sodium bicarbonate use could worsen long term survival with favorable neurological recovery among patients with out-of-hospital cardiac arrest. *Resuscitation*. 2017;119:63–69. [PubMed: 28802878]

67. Velissaris D, Karamouzos V, Pierrakos C, Koniari I, Apostolopoulou C, Karanikolas M. Use of sodium bicarbonate in cardiac arrest: Current guidelines and literature review. *J Clin Med Res.* 2016;8:277–283. [PubMed: 26985247]

68. Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S465–482. [PubMed: 26472996]

69. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation*. 2008;118:2452–2483. [PubMed: 18948368]

70. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive Care Med.* 2015;41:2039–2056. [PubMed: 26464394]

71. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome After cardiac arrest. *N Engl J Med.* 2002;346:549–556. [PubMed: 11856793]

72. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med.* 2002;346:557–563. [PubMed: 11856794]

73. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med.* 2013;369:2197–2206. [PubMed: 24237006]

74. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: A randomized clinical trial. *JAMA.* 2014;311:45–52. [PubMed: 24240712]

75. Kirkegaard H, Soreide E, deHaas I, et al. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest: A randomized clinical trial. *JAMA.* 2017;318:341–350. [PubMed: 28742911]

76. Lascarrou JB, Merdji H, Le Gouge A, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. *N Engl J Med.* 2019;381(24):2327–2337. 10.1056/NEJMoa1906661 [PubMed: 31577396] .

77. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med.* 2021;384(24):2283–2294. 10.1056/NEJMoa2100591
[PubMed: 34133859] .

78. Granfeldt A, Holmberg MJ, Nolan JP, et al. Targeted temperature management in adult cardiac arrest: Systematic review and meta-analysis. *Resuscitation*. 2021;167:160–172. 10.1016/j.resuscitation.2021.08.040
[PubMed: 34474143] .

79. Callaway CW, Coppler PJ, Faro J, et al. Association of initial illness severity and outcomes after cardiac arrest with targeted temperature management at 36 °C or 33 °C. *JAMA Netw Open*. 2020;3(7):e208215–e208215. 10.1001/jamanetworkopen.2020.8215
[PubMed: 32701158] .

80. Soar J, Nolan JP, Andersen LW, et al. Temperature Management in Adult Cardiac Arrest Consensus on Science with Treatment Recommendations. Brussels, Belgium: International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force, 2021 August 30. Available from: http://ilcor.org.

81. Elmer J, Polderman KH. Emergency neurological life support: Resuscitation following cardiac arrest. *Neurocrit Care*. 2017;27:134–143. [PubMed: 28913711]

82. Moskowitz A, Andersen LW, Rittenberger JC, et al. Continuous neuromuscular blockade following successful resuscitation from cardiac arrest: A randomized trial. *J Am Heart Assoc.* 2020;9(17):e017171–e017171. 10.1161/JAHA.120.017171
[PubMed: 32851921] .

83. May TL, Riker RR, Fraser GL, et al. Variation in sedation and neuromuscular blockade regimens on outcome after cardiac arrest. *Crit Care Med.* 2018;46(10):e975–e980. 10.1097/CCM.0000000000003301
[PubMed: 29979225] .

84. Anderson KB, Poloyac SM, Kochanek PM, et al. Effect of hypothermia and targeted temperature management on drug disposition and response following cardiac arrest: A comprehensive review of preclinical and clinical investigations. *Ther Hypothermia Temp Manag.* 2016;6(4):169–179. 10.1089/ther.2016.0003
[PubMed: 27622966] .

85. Perkins GD, Callaway CW, Haywood K, et al. Brain injury after cardiac arrest. *Lancet*. 2021;398(10307):1269–1278. 10.1016/S0140-6736(21)00953-3
[PubMed: 34454687] .

86. Mayasi Y, Geocadin RG. Updates on the management of neurologic complications of post-cardiac arrest resuscitation. *Semin Neurol.* 2021;41(4):388–397. 10.1055/s-0041-1731310
[PubMed: 34412143] .

87. Jozwiak M, Bougouin W, Geri G, et al. Post-resuscitation shock: Recent advances in pathophysiology and treatment. *Ann Intensive Care*. 2020;10(1):170–170. 10.1186/s13613-020-00788-z
[PubMed: 33315152] .

88. Sah Pri A, Chase JG, Pretty CG, et al. Evolution of insulin sensitivity and its variability in out-of-hospital cardiac arrest (OHCA) patients treated with hypothermia. *Crit Care*. 2014;18(5):586–586. 10.1186/s13054-014-0586-x
[PubMed: 25349023] .

89. Oksanen T, Skrifvars MB, Varpula T, et al. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. *Intensive Care Med.* 2007;33(12):2093–2100. 10.1007/s00134-007-0876-8
[PubMed: 17928994] .

90. François B, Cariou A, Clere-Jehl R, et al. Prevention of early ventilator-associated pneumonia after cardiac arrest. *N Engl J Med.* 2019;381(19):1831–1842. 10.1056/NEJMoa1812379
[PubMed: 31693806] .

91. McFadden ER, Jr., Warren EL. Observations on asthma mortality. *Ann Intern Med.* 1997;127:142–147. [PubMed: 9230005]

92. Petrillo TM, Fortenberry JD, Linzer JF, Simon HK. Emergency department use of ketamine in pediatric status asthmaticus. *J Asthma*. 2001;38:657–664. [PubMed: 11758894]

93. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: A systematic review with meta-analysis. *Thorax* 2005;60:740–746. [PubMed: 16055613]

94. Schultz TE. Sevoflurane administration in status asthmaticus: A case report. *AANA J.* 2005;73:35–36. [PubMed: 15727281]

95. Silverman RA, Osborn H, Runge J, et al. IV magnesium sulfate in the treatment of acute severe asthma: A multicenter randomized controlled trial. *Chest*. 2002;122:489–497. [PubMed: 12171821]

96. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA. The effect of heliox on nebulizer function using a beta-agonist bronchodilator. *Chest*. 1999;115:184–189. [PubMed: 9925082]

97. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest*. 2003;123:1018–1025. [PubMed: 12684289]

98. Soar J, Becker LB, Berg KM, et al. Cardiopulmonary resuscitation in special circumstances. *Lancet*. 2021;398(10307):1257–1268. 10.1016/S0140-6736(21)01257-5
[PubMed: 34454688] .

99. Brown SG, Blackman KE, Stenlake V, Heddle RJ. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. *Emerg Med J.* 2004;21:149–154. [PubMed: 14988337]

100. Mhyre JM, Tsen LC, Einav S, Kuklina EV, Leffert LR, Bateman BT. Cardiac arrest during hospitalization for delivery in the United States, 1998–2011. *Anesthesiology*. 2014;120:810–818. [PubMed: 24694844]

101. Jeejeebhoy FM, Zelop CM, Lipman S, et al. Cardiac arrest in pregnancy: A scientific statement from the American Heart Association. *Circulation*. 2015;132:1747–1773. [PubMed: 26443610]

102. Vanden Hoek TL, Morrison LJ, Shuster M, et al. Part 12: Cardiac arrest in special situations: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S829–S861. [PubMed: 20956228]

103. Roberts I, Shakur H, Folabi AA, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: An exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*. 2011;377(9771):1096–1101, 1101.e1–2. 10.1016/S0140-6736(11)60278-X
[PubMed: 21439633] .

104. Teeter W, Haase D. Updates in traumatic cardiac arrest. *Emerg Med Clin North Am.* 2020;38(4):891–901. 10.1016/j.emc.2020.06.009
[PubMed: 32981624] .

105. Seamon MJ, Haut ER, VanArendonk K, et al. An evidence-based approach to patient selection for emergency department thoracotomy: A practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg.* 2015;79:159–173. [PubMed: 26091330]

106. Link MS, Maron BJ, VanderBrink BA, Zhu W, Estes NA 3rd. Upper and lower limits of vulnerability to sudden arrhythmic death with chest-wall

impact (commotio cordis). *J Am Coll Cardiol.* 2003;41:99–104. [PubMed: 12570951]

107. Quan L, Mack CD, Schiff MA. Association of water temperature and submersion duration and drowning outcome. *Resuscitation*. 2014;85:790–794. [PubMed: 24607870]

108. Szpilman D, Webber J, Quan L, et al. Creating a drowning chain of survival. *Resuscitation*. 2014;85:1149–1152. [PubMed: 24911403]

109. Neumar RW, Otto CW, Link MS, et al. Part 8: Adult advanced cardiovascular life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S729–S767. [PubMed: 20956224]

110. Hoskins SL, doNascimento P, Jr., Lima RM, Espana-Tenorio JM, Kramer GC. Pharmacokinetics of intraosseous and central venous drug delivery during cardiopulmonary resuscitation. *Resuscitation*. 2012;83:107–112. [PubMed: 21871857]

111. Meaney PA, Bobrow BJ, Mancini ME, et al. Cardiopulmonary resuscitation quality: Improving cardiac resuscitation outcomes both inside and outside the hospital. A consensus statement from the American Heart Association. *Circulation*. 2013;128:417–435. [PubMed: 23801105]

112. Nolan JP, Berg RA, Bernard S, et al. Intensive care medicine research agenda on cardiac arrest. *Intensive Care Med.* 2017;43:1282–1293. [PubMed: 28285322]

SELF-ASSESSMENT QUESTIONS

1. Which rhythm is associated with the worst prognosis when noted as the first identifiable rhythm following a cardiac arrest?
   A. Asystole
   B. Pulseless electrical activity
   C. Pulseless ventricular tachycardia
   D. Ventricular fibrillation
2. Which of the following medications have been associated with an increase in survival to hospital discharge?
   A. Amiodarone
   B. Epinephrine
   C. Lidocaine
   D. Sodium bicarbonate
3. A 68-year-old patient suddenly grabs the chest and collapses to the ground in the grocery store. After confirming the patient is nonresponsive and activating EMS through your mobile phone, what is the next best step to take as a lay rescuer?
   A. Check for a pulse
   B. Open the airway and deliver 2 breaths
   C. Perform cycles of 30 compressions and 2 breaths until an AED arrives
   D. Perform chest compressions only and omit rescue breathing.
4. Early epinephrine administration is most beneficial following which rhythm?

A. Bradycardia

B. Pulseless electrical activity

C. Torsades de pointes

D. Ventricular fibrillation

5. The rationale for the administration of epinephrine during advanced cardiac life support measures is to increase which of the following?

A. Cardiac output

B. Coronary perfusion pressure

C. Heart rate

D. Oxygen demand

6. Randomized controlled trial data have demonstrated epinephrine to be associated with improvements in which of the following outcomes following a cardiac arrest?

A. Return of spontaneous circulation (ROSC)

B. ROSC and survival to hospital admission

C. ROSC, survival to hospital admission, and survival to hospital discharge

D. ROSC, survival to hospital admission, survival to hospital discharge, and survival to hospital discharge with good neurologic function

7. Which of the following is the drug of choice for torsades de pointes?

A. Adenosine

B. Amiodarone

C. Lidocaine

D. Magnesium sulfate

8. A 72-year-old patient presents to the ICU following the ROSC from a cardiac arrest secondary to a nonshockable rhythm. The patient did not regain consciousness and is subsequently intubated with a plan to implement targeted temperature management at 33°C (91.4°F) for 24 hours. Propofol and fentanyl infusions are prescribed for sedation and analgesia. Which adverse effect is most likely to occur upon rewarming?

A. Hyperglycemia

B. Hypokalemia

C. Hypotension

D. Prolongation of sedative medications

9. Which of the following is an acceptable therapy for asystole?

A. Amiodarone

B. Atropine

C. Defibrillation

D. Epinephrine

10. Successful resuscitation following PEA is largely dependent on

A. Administration of thrombolytics

B. Identification of the underlying cause

C. Rapid defibrillation

D. Therapeutic hypothermia

11. The postcardiac arrest care should address all of the following, EXCEPT:

A. Hypoxic brain injury

B. Myocardial dysfunction

C. Systemic ischemia reperfusion response

D. Renal impairment

12. A 79-year-old patient is admitted to the ICU following a cardiac arrest and remains comatose following the return of spontaneous circulation. The patient is subsequently intubated and sedated with a plan to implement targeted temperature management. The team would like to begin an antiseizure medication for seizure prophylaxis and asks what is the most appropriate regimen?

A. Levetiracetam

B. Phenytoin

C. Valproic acid

D. Seizure prophylaxis is not indicated

13. Which of the following is a potentially harmful effect of sodium bicarbonate?

A. Hyperkalemia

B. Intracellular acidosis

C. Tachycardia

D. Tissue hypoxia

14. Which parameter is the best indicator of high-quality CPR and most associated with ROSC following a cardiac arrest?

A. Arterial diastolic blood pressure >15 mm Hg

B. Arterial pH >7.2

C. End-tidal CO_2 >20 mm Hg (2.7 kPa)

D. Palpating a pulse during active chest compressions

15. A 62-year-old patient presents to the ICU following a cardiac arrest secondary to an acute myocardial infarction. ROSC was achieved followed by urgent cardiac revascularization. Echocardiography reveals an ejection fraction of 60% (0.6). After 24 hours, the patient remains in a comatose state and the team is very concerned about cerebral swelling. They would like to prioritize cerebral hemodynamics and blood flow to the brain. What

should the goal MAP be for this patient in the absence of advanced cerebral monitoring?

A. >50 mm Hg

B. >65 mm Hg

C. >80 mm Hg

D. >100 mm Hg

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** In general, nonshockable rhythms are associated with higher mortality rates compared to shockable rhythms. Between the nonshockable rhythms, asystole, and PEA, the survival for asystole is roughly 2% compared to 10% for PEA. This is described in the "Epidemiology" section.

2. **B.** Epinephrine has been associated with increased rates of ROSC, hospital admission and hospital survival. Survival with good neurologic function however is not improved. Both amiodarone and lidocaine have been associated with increased rates of survival to hospital admission but not discharge. Sodium bicarbonate has not been shown to increase ROSC or survival. This is described in the "Pharmacologic Therapy" section.

3. **C.** After assessing responsiveness, calling for help and activating EMS, the lay rescuer should begin chest compressions using a ratio of 30 compressions:2 breaths. If a lay rescuer is unwilling to administer rescue breaths, then chest compression-only CPR can be initiated. With arrests of prolonged duration though, arterial oxygen content will decrease if ventilations are withheld. Pulse checks are not recommended for lay rescuers because they lead to delays in the provision of chest compressions. Chest compressions should occur before ventilations consistent with the C-A-B teaching approach for CPR. This is described in the "Sequence of Resuscitation–Basic Life Support" section.

4. **B.** Early epinephrine has been shown to be most beneficial in patients with asystole or PEA. It is now a point of emphasis on current treatment algorithms. This is described in the subsection "Vasopressors" under the "VF/PVT–Pharmacologic Therapy" section and under "Pharmacologic Therapy" in the "Pulseless Electrical Activity and Asystole" section.

5. **B.** CPR provides necessary oxygen to the heart and the brain but the perfusion pressures encountered are not high enough to reach thresholds that have been associated with ROSC. Epinephrine is therefore added to increase coronary perfusion pressure through its effects on alpha-receptors. The beta-adrenergic effects of epinephrine can lead to increased heart rate, increased cardiac output, and increased myocardial oxygen demand which can be detrimental in the post-resuscitation phase. The rationale for epinephrine is explained in the subsection "Vasopressors" under the section "Pharmacologic Therapy."

6. **C.** In a landmark randomized controlled trial (PARAMEDIC 2) comparing epinephrine with placebo, epinephrine was associated with improvements in ROSC, survival to hospital admission and survival to hospital discharge but there was no improvement in survival with good neurologic function. This was the first RCT demonstrating survival to hospital discharge with vasopressor therapy. This is described in the subsection "Vasopressors" under the section "Pharmacologic Therapy."

7. **D.** The drug of choice for torsades de pointes is magnesium sulfate. This is the only indication for routine magnesium administration in cardiac arrest. This is listed in the "Magnesium" subsection of the "VF/PVT–Pharmacologic Therapy" section.

8. **D.** Hypothermia achieved via targeted temperature management can lead to a decrease in drug metabolism and clearance. This can largely impact sedative and analgesic medications and interfere with prognostication. Hypothermia can also lead to intracellular shifts of potassium and decreased sensitivity to insulin leading to hypokalemia and hyperglycemia. Upon rewarming, potassium is released back into extracellular compartment (increasing the risk for hyperkalemia), and insulin sensitivity increases (increasing the risk for hypoglycemia). Hypotension is not a frequent adverse event associated with rewarming. This is described in the subsection "Targeted Temperature Management" under "Postresuscitative Care".

9. **D.** Asystole is a nonshockable rhythm that often represents confirmation of death. Therapy consists of chest compressions, epinephrine administration, and identification of the underlying cause. This is explained in the "Pharmacologic Therapy" section under PEA/Asystole.

10. **B.** Successful resuscitation of PEA is largely dependent on the identification of the underlying cause. These can be remembered using the mnemonic 6 H's and 6 T's. These are listed in Table 41-2.

11. **D.** The postcardiac arrest care should address hypoxic brain injury, myocardial dysfunction, systemic inflammation, and the underlying cause of the arrest. While renal impairment may be an important comorbidity and impact care delivery, it is not among the four essential elements of postcardiac care. These are described in Table 41-3.

12. **D.** While seizures can occur in the post-resuscitation phase, studies have not demonstrated a benefit with prophylactic antiseizure medications. Prophylaxis is therefore not indicated. This is further described in the "Seizures" subsection of "Postresuscitative Care."

13. **B.** Deleterious effects of sodium bicarbonate administration include intracellular acidosis, hypokalemia, tissue hypercarbia, and overshoot alkalosis. This is described in the "Acid/Base Management" section.

14. **C.** End-tidal CO_2 is a measurement of carbon dioxide excretion obtained from the lungs. As cardiac output (obtained through high-quality CPR) increases, the delivery of CO_2 from the peripheral tissues to the lungs increases. End-tidal CO_2 >20 mm Hg (2.7 kPa) has been associated with higher rates of ROSC. Arterial diastolic blood pressure can be a surrogate for coronary perfusion pressure but goals should be >25 mm Hg. Arterial pH and palpating a pulse during CPR have not been linked to ROSC. This is explained in the "Evaluation of Therapeutic Outcomes" section.

15. **C.** In settings where advanced cerebral monitoring is not routine and increased intracranial pressure is suspected, target MAP values that exceed 80 mm Hg may be required. This is done to increase cerebral perfusion pressure which is calculated as MAP minus ICP. In settings where advanced cerebral monitoring is performed, MAP goals can be individualized accordingly. This is explained in the "Evaluation of Therapeutic Outcomes" section.