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Resuscitation After Cardiac Arrest
A 3-Phase Time-Sensitive Model

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DESPITE 40 YEARS OF CARDIOPULMONARY RESUSCITATION (CPR) therapies, overall survival rates after cardiac arrest remain poor. Recent data suggest that the death toll in the United States is greater than previously believed—possibly 450 000 sudden deaths each year—yet the average survival rate remains lower than 5%.[1] In contrast, the article by Cobb et al[2] in this issue of THE JOURNAL suggests a lower incidence rate, about 184 000 cardiac arrests per year, as well as a decreasing proportion of cardiac arrests with ventricular fibrillation (VF) as the first identified rhythm.

Current International Liaison Committee on Resuscitation (ILCOR) guidelines promulgate rhythm-based therapies during cardiac arrest.[3] These well-known treatment algorithms are static in the sense that they do not consider the passage of time. For example, VF is treated uniformly (with immediate defibrillation) whether the duration is 1 minute or 15 minutes. When this approach is unsuccessful after 3 attempts at defibrillation, rescue breathing and cardiac compression are initiated, followed by drug therapies and repeated defibrillation attempts. However, emerging data suggest that this approach is not optimal for all patients and that current guidelines for immediate defibrillation may be contraindicated in some patients, especially as the duration of cardiac arrest increases and the pathophysiology of ischemia/reperfusion progresses over time.

This article proposes a 3-phase model of CPR to reflect the time-sensitive progression of resuscitation physiology, which in turn requires time-critical interventions. The model suggests that the optimal treatment of cardiac arrest is phase-specific and includes (1) the electrical phase, which extends from the time of cardiac arrest to approximately 4 minutes following the arrest; (2) the circulatory phase, from approximately 4 to approximately 10 minutes after cardiac arrest; and (3) the metabolic phase, extending beyond approximately 10 minutes after cardiac arrest. Importantly, in this model the term *phase* is designated for the maximally effective and most critical initial therapy for that period. However, the time boundaries between phases are approximate and not precisely defined in the current literature.

See also p 3008.

THE ELECTRICAL PHASE

With the advent of the internal cardiac defibrillator and rapid external defibrillation, the value of early defibrillation for patients with out-of-hospital VF and cardiac arrest has been established.[4] Early defibrillation is currently an ILCOR (and European Resuscitation Council and American Heart Association)[3] class I recommendation; it has excellent supporting animal and human data. An example of the efficacy of defibrillation during the electrical phase (from cardiac arrest until approximately 4 minutes) is the success of the implantable cardioverter defibrillator (ICD), which provides defibrillation within 15 to 20 seconds of the onset of VF and rarely fails to restore organized electrical activity. A meta-analysis of 3 large secondary prevention trials comparing the ICD to amiodarone revealed the superiority of ICDs with less all-cause mortality and decreased arrhythmias, particularly in patients with reduced cardiac ejection fraction.[4]

The foundation for the success of early external defibrillation during the electrical phase was reported in the early 1980s, when time-vs-survival curves for large populations showed the deleterious effects of time on survival, such that each passing minute decreased survival by 8% to 10%.[5,6] Studies using automated external defibrillators (AEDs) to achieve rapid defibrillation (ie, within 4 minutes of cardiac arrest) have demonstrated improved survival in a variety of settings and situations, including police rescuers trained in early defibrillation,[7-10] casino security personnel trained with AEDs,[11] airport personnel and nontrained members of the public in airports using AEDs,[12,13] in-flight airline personnel,[14-16] and a broad community-based defibrillation program that included lay rescuers, police, and public AEDs.[17] Collectively, the effectiveness of early defibrillation is well established and can result in survival rates approaching 50%, and this electrical phase therapy is exactly what is practiced now for VF following any duration of cardiac arrest.

THE CIRCULATORY PHASE

In the circulatory phase (from approximately 4 to approximately 10 minutes of VF), the most important lifesaving

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therapy may be to initiate a technique to first provide oxygen delivery (chest compression/ventilation under current guidelines), followed by defibrillation (ie, delaying defibrillation by 1-3 minutes). While this circulatory phase is easy to envision from a theoretical perspective, optimal implementation of such an approach is complex and would require development of a reliable device or method to determine the time elapsed since collapse.

Data from animal experiments support the concept of a circulatory phase, in which chest compression (and tissue oxygen delivery) take priority over defibrillation.[18-26] In an animal model in which the duration of VF varied (1, 3, 5, or 9 minutes) prior to defibrillation, Yakaitis et al[21] found that immediate defibrillation was only optimal when performed in 3 minutes or less. Cardiopulmonary resuscitation plus epinephrine resulted in better survival when performed after 5 or 9 minutes of untreated VF compared with immediate countershock or with CPR alone for 1 minute followed by countershock. After 5 minutes of cardiac arrest, immediate defibrillation resulted in 30% successful defibrillation (3/10) and 0% return of spontaneous circulation (ROSC) (0/10), whereas 1 minute of CPR plus epinephrine before defibrillation resulted in 70% successful defibrillation (7/10) and 40% ROSC (4/10). Niemann et al[19] reported that after 7.5 minutes of untreated VF in animals, 5 minutes of CPR plus epinephrine resulted in a significant improvement in survival compared with immediate defibrillation (64% [9/14] vs 21% [3/14] survival). In contrast, after a shorter (5-minute) period of untreated VF, use of CPR first failed to provide any benefit over immediate defibrillation.[20] Menegazzi et al[22] demonstrated that after 8 minutes of untreated VF, CPR plus a drug cocktail (including epinephrine, lidocaine, bretylium, and propanolol) resulted in 77% ROSC compared with 22% ROSC with immediate defibrillation. In a study comparing different defibrillation waveforms delivered after 6 minutes of VF with or without CPR (compression and ventilation) first, Garcia et al[18] showed that no animal with defibrillation first (0/12) established a perfusing rhythm with either waveform, whereas if CPR was provided prior to defibrillation, 46% (11/24) established a perfusing rhythm. Yu et al[26] reported that after 7 minutes of untreated VF in swine, the length of time that CPR was withheld immediately prior to shock (to allow the AED to analyze rhythm and charge) was correlated with outcome—the longer the withholding of CPR prior to defibrillation, the worse the survival rate. Interruptions of CPR prior to defibrillation of 3, 10, 15, and 20 seconds resulted in a dose-dependent decrease in ROSC of 100%, 80%, 40%, and 0%, respectively. Collectively, these animal studies suggest that immediate defibrillation for VF beyond approximately 4 to 5 minutes is not an optimal therapy and may be contraindicated in these conditions.

Two clinical studies suggest that the same survival effect may hold true in humans. Cobb et al[24] studied the effects of immediate vs delayed countershock (while starting CPR first) in emergency medical services–attended cardiac arrests by comparing survival rates in Seattle, Wash, during 2 periods. In the first, standard "defibrillation first" guidelines were used and overall survival was 24%; in the second period, 90 seconds of CPR was performed prior to defibrillation and overall survival was 30%. Subgroup analysis showed that immediate defibrillation was superior (but not significantly so) to providing 90 seconds of CPR within the first 3 minutes following cardiac arrest, but after 3 minutes, providing 90 seconds of CPR followed by defibrillation was superior. In a randomized study from Oslo, Wik et al[25] reported an improvement in survival to hospital discharge of 22% (14/64) vs 4% (2/55) as well as 1-year survival of 20% (13/64) vs 4% (2/55) after cardiac arrest in the circulatory phase (ie, >5 minutes after collapse) when CPR was performed first for 3 minutes prior to defibrillation (ie, defibrillation was delayed 3 minutes).

The physiological mechanism underlying this observation is unknown but is consistent with the notion that defibrillation of the globally ischemic heart beyond about 4 minutes may be detrimental. Outcomes appear to be improved when defibrillation is briefly delayed in favor of providing some limited circulation of blood with partial restoration of substrates including oxygen, or washout of deleterious metabolic factors that have accumulated during ischemia. This change in therapy could affect a large number of cardiac arrest cases because only a minority of patients are currently attended by rescuers within 4 minutes of arrest (ie, in the electrical phase), and far greater numbers of patients are treated during the circulatory phase.

THE METABOLIC PHASE

After approximately 10 minutes of cardiac arrest, the effectiveness of both immediate defibrillation and CPR followed by defibrillation decreases rapidly and survival rates appear poor. It is unknown whether irreversible injury occurs or whether therapeutic approaches fail to correct important factors in this phase.

During the metabolic phase (after approximately 10 minutes of arrest), tissue injury from global ischemic events and from reperfusion can result in circulating metabolic factors that cause additional injury beyond the effects of local or focal ischemia. Gut mucosal translocation of gram-negative bacteria may result in endotoxin- and cytokine-induced suppression of myocardial function after defibrillation.[27] Differences in circulating levels of interleukins and tumor necrosis factor and immunological alterations similar to the sepsis state have been reported in survivors compared with nonsurvivors.[28] Global whole-body ischemia appears far worse for organ recovery than does regional ischemia. Peripheral vasoconstrictors, which are helpful during the circulatory phase, may cause organ ischemia, particularly in the splanchnic bed, and may lead to decreased survival during the metabolic phase.

In the metabolic hypothesis, reperfusion events can contribute to cell death and diminished organ function independent of the adverse effects of ischemia. Cellular studies involving ischemia and hypothermia suggest that control of these

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deleterious processes even after a period of ischemia (ie, during the "reperfusion" interval) may result in clinical improvement. Vanden Hoek et al[29,30] demonstrated that isolated perfused cardiomyocytes show accelerated cell death, release of cytochrome C, and initiation of apoptosis only after reperfusion but not during prolonged ischemia. Cell death in this model was reduced by 60% if the temperature of these cardiac cells was lowered from 37°C to 25°C immediately after reperfusion. However, the best cellular protection (decreasing cell death by 73%) occurred when cooling was performed prior to reperfusion, even if reperfusion with oxygenated media plus substrate was delayed for 10 minutes to allow time for cooling (ie, cooling first, then reperfusion).[31] These findings suggest that cellular reperfusion injury in which ischemia alone is not responsible for cell death, rather the conditions of reperfusion (ie, restoring oxygen and substrates), contribute to cell death (at least 73% within this cellular model). A possible protective mechanism may involve hypothermia-mediated attenuation of the rapid oxidant burst observed with reperfusion. This challenges the current practice of immediate reperfusion for all ischemic conditions.

Additional mechanisms for reperfusion injury, such as entry of calcium, alterations in sodium, and inflammation, may offer additional opportunities for metabolic control in the postresuscitation period. Caspase inhibitors and other apoptosis inhibitors may be able to improve cellular function during reperfusion.[30,32] Other metabolic and biochemical interventions are likely to be effective in this metabolic phase of cardiac arrest and represent an important area of future research.[33,34]

Two human studies also suggest the value of metabolic-focused treatment during the metabolic phase of cardiac arrest.[35,36] In a study of controlled reperfusion, in which patients received cardiopulmonary bypass with a decompressed heart and alteration of blood composition by using metabolic therapies including an amino acid–enriched solution with buffer, low calcium, increased potassium, and high dextrose, as is done routinely during open-heart operations, Beyersdorf et al[36] treated 14 patients with in-hospital cardiac arrest with intractable VF for 22 to 150 minutes after failed standard advanced cardiopulmonary life support therapy. After stabilization with controlled reperfusion, correction of cardiac pathology (coronary or valve lesions) when possible, and support using bypass and then attempted weaning, 13 of 14 patients were resuscitated with ROSC and functional cardiac activity. Ejection fraction improved over preoperative status, and 11 of 14 survived to hospital discharge, with only 2 sustaining neurological damage. In a second study involving 12 patients who developed cardiac arrest from acute myocardial infarction or unstable angina (either in the cardiac catheterization laboratory or en route to the operating room), underwent unsuccessful resuscitation using advanced cardiopulmonary life support, and had prolonged CPR until resuscitation was attempted using controlled reperfusion, 10 of the 12 patients were discharged from the hospital neurologically intact.[35] The authors suggest that institution of cardiopulmonary bypass ensured adequate systemic blood flow while simultaneously allowing the dilution of circulatory toxic metabolic factors, with both factors critical to outcome. Although this promising therapy requires further study, it is costly, invasive, and clearly not appropriate for all patients who are unresponsive to resuscitative attempts.

Recent studies have shown an improvement in neurologically intact survival after out-of-hospital cardiac arrest (49% survival compared with 26%[37] and 55% good neurological outcome vs 39%[38]) when external cooling to 32°C to 34°C was performed in comatose but hemodynamically stable survivors of cardiac arrest. Patients were cooled relatively late following cardiac arrest—hours after return of circulation and long after the ischemic insult. This suggests some ongoing injury in the brain despite the return of circulation (ie, circulation alone is not sufficient for optimal outcome), and that metabolic intervention, in this case hypothermia, still provides some protection even when delayed for hours after cardiac arrest.

In contrast, several clinical trials using high-dose epinephrine, which has been shown to be effective in experimental animals, have shown no better results than low- or standard-dose epinephrine in cardiac arrest in humans. This difference in outcome may reflect animal studies conducted in the circulatory phase (cardiac arrest intervals of 4-10 minutes), whereas use of epinephrine in humans is typically delayed beyond 10 minutes, primarily occurring in the metabolic phase. These observations, along with the proposal that peripheral ischemia induces metabolic circulating factors, suggests that early higher-dose epinephrine may be beneficial during the circulatory phase (as seen in animals) but detrimental when given later in the metabolic phase. High-dose epinephrine may increase gut ischemia injury and lead to sepsis following restoration of flow.[28] If true, this is problematic for current guidelines for routine use of epinephrine during this late metabolic phase.

LIMITATIONS

A requirement for the practical use of a 3-phase model is for clinicians to accurately know what phase a person is in following an unwitnessed cardiac arrest or an unknown ischemic interval, highlighting the importance of aggressive bioengineering and device development for resuscitation.[33,34] New technologies, such as electrocardiographic analysis of VF for spectral and waveform characteristics,[39,40] reactive oxygen or nitrogen species detectors,[41] rapid ion concentration measurements, and proteomic detectable signaling markers,[42] may allow accurate estimation of time of ischemia and best treatment option. Another limitation of the 3-phase model is that it addresses the physiology of only VF-mediated cardiac arrest. The time-sensitive concept may be similar for trauma-induced or hypoxic-mediated cardiac arrest, which is the most common etiology of arrest in children and younger persons. As highlighted by the report by Cobb et al, a decreasing proportion of patients are treated with VF, more patients have either asystolic arrest or pulseless electrical activity (PEA), and

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many patients develop postdefibrillation PEA/asystole, which is uniformly associated with poorer survival rates than VF.[2] However, few data are available to suggest how or whether the time-sensitive model would be applied to PEA/asystole.

CONCLUSION

The proposed 3-phase model of resuscitation highlights the need for time-sensitive ischemia/reperfusion therapy and includes an electrical phase, a circulatory phase, and a metabolic phase. The model is based on emerging evidence that current guidelines for treatment of cardiac arrest reflect a limited view of the pathophysiology of arrest and resuscitation and suggests that distinct phase-specific initial therapy is necessary to improve survival for patients with VF.

Phase-specific research is needed to extend knowledge of the importance of time on resuscitation, such as testing early defibrillation and public access defibrillation programs during the electrical phase and testing chest compression and vasoconstrictors first during the circulatory phase. Future studies of potential usefulness of cardiopulmonary bypass are inappropriate for the electrical phase but might be of value for the metabolic phase. Use of specific drugs and prompt metabolic interventions such as hypothermia should be tested in a phase-specific manner as well. The use of this 3-phase model may help promote additional basic research on prolonged ischemia, reperfusion physiology, and reversible metabolic factors, as well as applied and engineering research, particularly with new insight and understanding of the biochemical pathways associated with ischemia and reperfusion and new technology for artificial circulation. Research should include translational studies that integrate newer cellular biology within a resuscitation practice.

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