SPECIAL CONTRIBUTIONS

Bench to Bedside: Resuscitation from Prolonged Ventricular Fibrillation

MARK G. ANGELOS, MD, JAMES J. MENEGAZZI, PHD, CLIFTON W. CALLAWAY, MD, PHD

Abstract. Ventricular fibrillation (VF) remains the most common cardiac arrest heart rhythm. Defibrillation is the primary treatment and is very effective if delivered early within a few minutes of onset of VF. However, successful treatment of VF becomes increasingly more difficult when the duration of VF exceeds 4 minutes. Classically, successful cardiac arrest resuscitation has been thought of as simply achieving restoration of spontaneous circulation (ROSC). However, this traditional approach fails to consider the high early post–cardiac arrest mortality and morbidity and ignores the reperfusion injuries, which are manifest in the heart and brain. More recently, resuscitation from cardiac arrest has been divided into two phases; phase I, achieving ROSC, and phase II, treatment of reperfusion injury. The focus in both phases of resuscitation remains the heart and brain, as prolonged VF remains primarily a two-organ disease. These two organs are most sensitive to oxygen and substrate deprivation and account for the vast majority of early post-resuscitation mortality and morbidity. This review focuses first on the initial resuscitation (achieving ROSC) and then on the reperfusion issues affecting the heart and brain. **Key words:** ventricular fibrillation; cardiac arrest; resuscitation; heart; brain. ACADEMIC EMERGENCY MEDICINE 2001; 8:909–924

VENTRICULAR fibrillation (VF) remains the most frequent arrhythmia associated with human cardiac arrest. Despite a well-defined treatment modality, defibrillation, the overall survival rate from an out-of-hospital VF cardiac arrest remains very low. The window of time for successful resuscitation with defibrillation alone is very narrow—lasting only a few minutes. Generally this time is less than the time required to bring a defibrillator to the patient. Beyond this brief time window of a few minutes, therapies in addition to defibrillation are frequently needed. Classically, resuscitation has primarily been thought of as achieving restoration of spontaneous circulation (ROSC). More recently, resuscitation from cardiac arrest has been divided into two phases. The first phase of resuscitation is obtaining ROSC and the second phase is supporting heart and brain dysfunction in the early reperfusion period (Fig. 1). The focus in both phases of resuscitation remains the heart and brain, as prolonged VF remains primarily a two-organ disease. These two organs are most sensitive to oxygen and substrate deprivation and account for the vast majority of early post-resuscitation mortality and morbidity. In this review we focus first on the initial resuscitation (achieving ROSC) and then on the reperfusion issues affecting the heart and brain. An understanding of heart and brain reperfusion is critical in designing future successful therapies for resuscitation from prolonged episodes of VF.

From the Department of Emergency Medicine, Ohio State University (MGA), Columbus, OH; and the Department of Emergency Medicine, University of Pittsburgh (JJM, CWC), Pittsburgh, PA.

Section editors: Charles B. Cairns, MD, Division of Emergency Medicine, University of Colorado Health Sciences Center, Denver, CO, and Edward A. Panacek, MD, Division of Emergency Medicine, UC Davis Medical Center, Sacramento, CA.
Received May 15, 2001; accepted May 23, 2001.

Address for correspondence and reprints: Mark G. Angelos, MD, Department of Emergency Medicine, The Ohio State University, 016 Prior Health Sciences Library, 376 West Tenth Avenue, Columbus, OH 43210-1270; Fax: 614-292-7658; e-mail: angelos.1@osu.edu

PHASE I: ACHIEVING ROSC

Initial Resuscitation. Initial resuscitation of the heart from VF has the goal of restoring organized electrical and contractile function. Defibrillation is the only advanced life support (ALS) intervention that works, but it is extremely time-sensitive. The success rate for defibrillation declines by approximately 10% per minute of VF.[1–3] The most recent Advanced Cardiac Life Support (ACLS) guidelines continue to espouse immediate defibrillation as the initial therapeutic intervention for the treatment

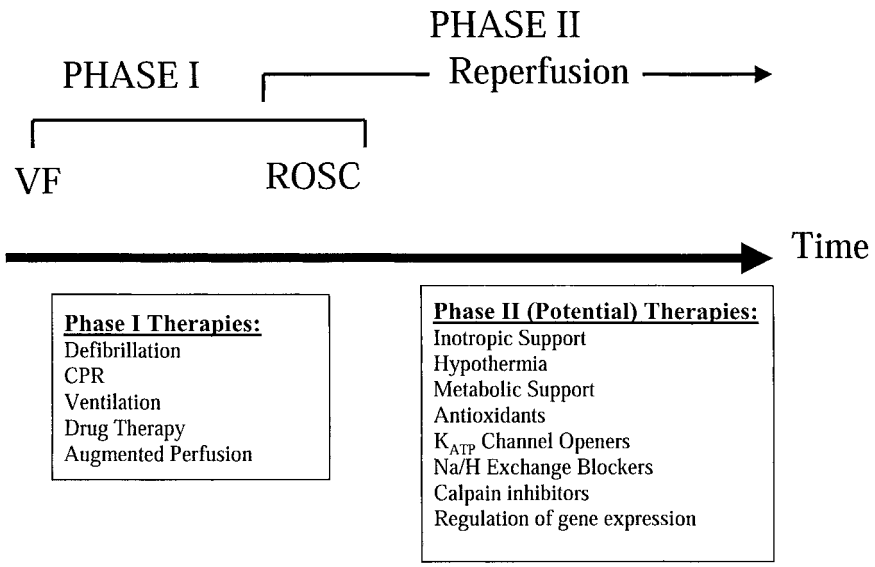

Figure 1. Resuscitation from prolonged ventricular fibrillation (VF) consists of first achieving restoration of spontaneous circulation (ROSC) (phase I resuscitation) followed by heart and brain resuscitation (phase II resuscitation). Optimal therapy during phase II ultimately will have to begin during phase I for best results, as significant reperfusion injury happens within the first minutes of reperfusion. CPR = cardiopulmonary resuscitation; K_{ATP} = adenosine triphosphate = sensitive potassium; NA/H = sodium/hydrogen.

of all cases of VF and pulseless ventricular tachycardia.[4] Defibrillation is to be repeated up to three times before any other intervention is attempted. The rationale for using three *stacked* shocks would seem to be supported by the fact that transthoracic impedance decreases with each subsequent shock.[5–7] Theoretically, this drop in impedance should result in more energy being delivered to the myocardium and a greater likelihood of affecting a critical mass of myocardial tissue.

But does the likelihood of successful defibrillation in humans increase during the first three countershocks? A report from Hargarten et al., which summarizes the results of defibrillation during a ten-year period in Milwaukee, suggests otherwise.[8] They looked at the results of the first three defibrillation attempts in 1,497 patients with witnessed, coarse VF. Of these patients, only 12% had a pulse restored after the first defibrillation, while 34% had an electrocardiogram (ECG) rhythm change to asystole or pulseless electrical activity (PEA). Since asystole and PEA are generally more refractory to resuscitation than VF, it can be argued that having an ECG change from VF to either asystole or PEA is a negative outcome. So the odds ratio for having an unfavorable ECG rhythm change to having pulses restored is 2.8 for the first shock. After the second shock, 4% had pulses restored, while 16% converted to asystole/PEA (odds ratio of 4.0). Following the third shock, 2% got a pulse back, while 8% went from VF to asystole/PEA (odds ratio 4.0). Overall, the empiric use of three consecutive shocks for the initial treatment of VF resulted in 18% of patients' having pulses restored, but the majority (58%) had ECG conversion to asystole/PEA. Thus, while the first defibrillation was associated with the greatest likelihood of success, the second and third shocks had rapidly diminishing returns. So, in spite of the fact that transthoracic impedance has been reported to decrease with subsequent shocks, the clinical use of using three *stacked* shocks of increasing energy did not result in increased defibrillation success. Indeed, using three consecutive shocks without other interventions interspersed may increase the likelihood of putting patients into asystole or PEA. The strategy of delivering three successive defibrillation attempts prior to any other ALS interventions should be questioned.

Defibrillation-induced Myocardial Injury. Defibrillation is not an innocuous therapy. Passing electrical current through the myocardium has been demonstrated to cause both microscopic and macroscopic lesions, including myocardial necrosis.[9,10] Defibrillation has also been shown to adversely affect enzyme activity,[11] produce lactate,[12] increase mitochondrial dysfunction,[13] and decrease myocardial contractility.[14] Interestingly, above a certain threshold, increased shock energy can actually decrease the efficacy of defibrillation.[15] Thus, the optimum energy level for defibrillation should have the highest likelihood of success, while causing the minimum amount of myocardial damage. Various defibrillation waveforms differ in efficacy at a given dose of energy, prompting the question what is the best defibrillation waveform for use in the initial resuscitation of VF?

Monophasic vs Biphasic Waveforms. Most *transthoracic* defibrillators in use today deliver monophasic defibrillation waveforms. This technology has remained relatively unchanged for the past 30 years. Monophasic waveforms have only a positive current; thus, the shape of the waveform is determined by the speed and slope at which the energy rises and falls. All monophasic waveforms begin with a positive upslope in current. If the current gradually returns to zero, the shape is described as being "damped sinusoidal." If the waveform drops instantly to zero, it is called "truncated exponential." In contrast, biphasic waveforms, on the other hand, have both a positive phase and a negative phase. Current is first pulsed in the positive direction, then the energy flow is reversed and crosses zero into the negative direction (Fig. 2).

While biphasic waveform use is relatively new, it has been extensively researched during the past 17 years.[16–19] Biphasic defibrillation has been shown to have superior defibrillating properties for both internal[18,20–22] and external defibrillation.[23,24] Biphasic waveforms require less energy to achieve effective defibrillation when compared with monophasic waveforms.[21–24] Biphasic defibrillation is also associated with less post-shock myocardial damage and dysfunction at equivalent energy levels.[25–27] A multicenter trial comparing truncated biphasic shocks with monophasic damped sine waveform shocks was conducted in patients during automated implantable cardioverter defibrillator (AICD) surgery. Transthoracic shocks of 130 J biphasic were compared with 200-J monophasic shocks. This study showed that the two energy levels and waveforms produced similar first-shock successes, but that the biphasic group demonstrated fewer post-shock ECG abnormalities.[28] This study suggests that biphasic waveforms seem to be superior to monophasic waveforms on all fronts. However, most of the studies cited above were conducted in electrophysiology labs studying VF of very short duration (15–30 seconds). It is not immediately clear whether these findings can be extrapolated to prolonged VF as is encountered in the out-of-hospital arena.

Two recent studies have compared biphasic and monophasic transthoracic defibrillations in swine models of prolonged VF. The first study delivered escalating doses (first shock 2.5 J/kg, second shock 3.5 J/kg, and third shock 4.5 J/kg) of energy for both waveforms after 8 minutes of untreated VF, plus 1 minute of external chest compression and oxygen ventilation.[29] This study showed that biphasic defibrillation (7/17) produced a superior rate of ROSC when compared with monophasic defibrillation (1/17), but there was no difference in one-hour survival rates. The second study compared a fixed dose of biphasic defibrillation (150 J first three shocks) with an escalating dose of mon-

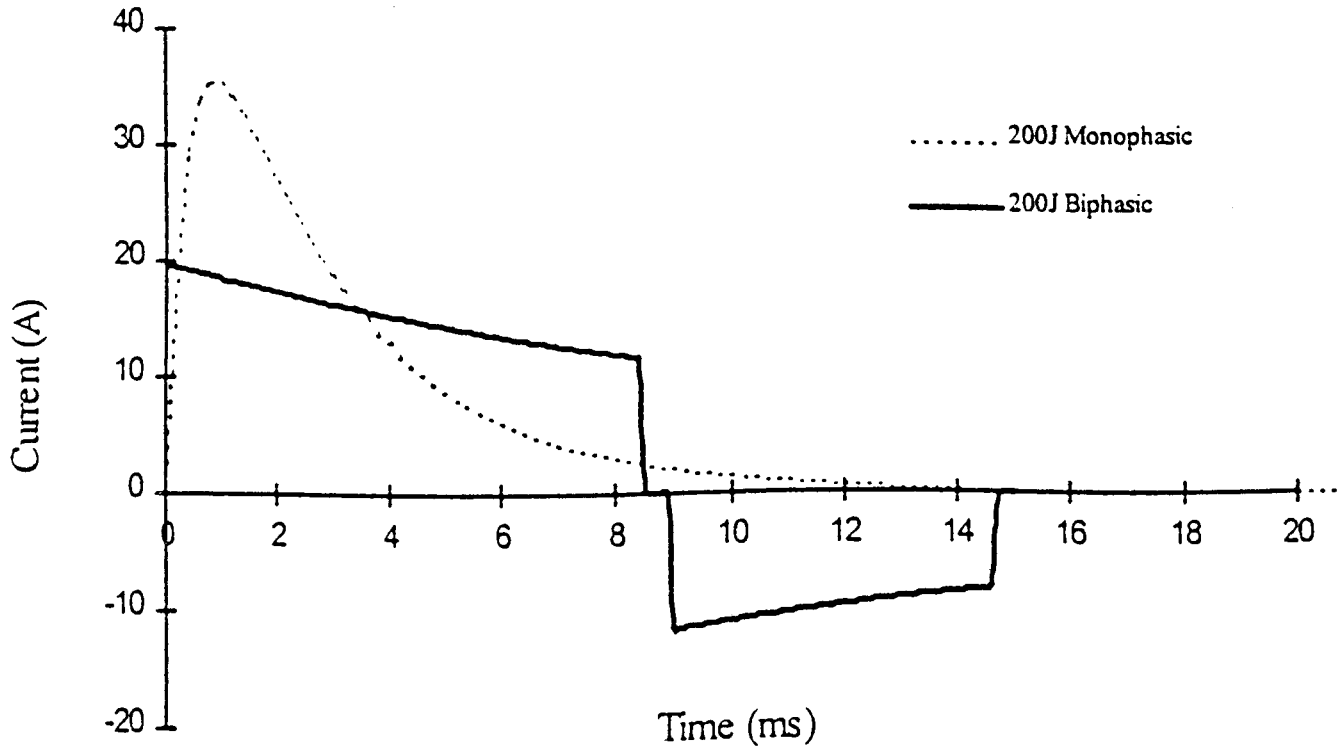

Figure 2. The biphasic and damped sinusoidal waveforms used as delivered to a 75-ohm impedance. Reprinted with permission from: Scheatzle MD, Menegazzi JJ, Allen TL, Durham SB. Evaluation of biphasic transthoracic defibrillation in an animal model of prolonged ventricular fibrillation. Acad Emerg Med. 1999; 6:880–6.

ophasic defibrillation (200 J, 300 J, and 360 J) after 5 minutes of untreated VF.[30] This study demonstrated that the two waveforms produced similar first-shock success rates (i.e., terminated VF) and similar incidences of post-shock PEA with subsequent shocks. There was also no difference in the numbers of animals that were successfully resuscitated. Taken together, these studies suggest biphasic defibrillation is at least as good as monophasic defibrillation. If, however, there is a safety advantage to the use of biphasic waveform defibrillation, this would seem to confer an advantage to biphasic defibrillation over monophasic defibrillation.

The first biphasic automated external defibrillator (AED) was approved for use in the United States in 1996. These devices use a fixed dose (150 J) of energy for all shocks. An early post-market surveillance study showed that the devices terminated VF at a high rate, when used on victims of out-of-hospital cardiac arrest.[31] In this study, the authors report a first-shock successful rhythm conversion rate of 89%, but an ROSC rate of only 56%. However, such reports must be interpreted with care. Many studies utilize definitions of "successful" that include ECG rhythm changes to PEA and even asystole. While electrophysiologists might consider these rhythms successful because they terminate VF in the isolated setting of the electrophysiological laboratory, most emergency physicians would consider these to be less than successful because patients in these rhythms so rarely survive to hospital discharge.

Defibrillation Energy Levels. It remains unclear whether low fixed, high, or escalating doses of energy are most effective. One recent study in humans compared higher-energy transthoracic biphasic defibrillation (200 J) with low-energy biphasic (130 J) and monophasic defibrillation at 200 J.[32] Conducted during AICD testing, the duration of VF was again of short duration (mean ± SD 19 ± 10 seconds). Higher-energy biphasic defibrillation produced better first-shock results with a 100% success rate (39/39 attempts), compared with low-energy biphasic (83%, 39/47) and monophasic (90%, 61/68) waveforms. These defibrillation rates of the monophasic and low-energy biphasic waveforms were not significantly different from each other. At this writing, these data are the first evidence that increasing biphasic energy for the first shock may improve defibrillation success rates. Again, because the VF episodes were of very short duration, these results may not be transferable to the type of VF that is encountered in the out-of-hospital environment.

In summary, biphasic waveform defibrillation has become the industry standard for AICD use, but these devices are designed to treat VF of very short duration. There are very few studies directly comparing biphasic and monophasic defibrillations for the treatment of *prolonged VF*, and these have shown no substantial differences in outcomes. Biphasic waveforms might have a safety advantage over monophasic, but few studies have compared similar doses of energy (making it difficult to determine whether it is the waveform or the lower energy that is responsible for decreased damage/dysfunction). It is not presently known which waveform is superior for defibrillating the human heart after prolonged VF. Futhermore, the optimum energies for defibrillation, regardless of waveform, have not yet been determined.

Analysis of VF Waveform to Discriminate Early VF and Prolonged VF. The problem, of course, is that in the emergency setting, the duration of VF is rarely known with any certainty or reliability. One exception is when the onset of VF is actually witnessed by health care providers. In these limited cases, immediate defibrillation is always the initial treatment of choice. But what about the more typical cases where a call for an apneic, pulseless patient is received by an emergency medical services (EMS) dispatch unit and an ALS ambulance cannot reach the patient for 6 or 8 minutes? Advanced Cardiac Life Support training suggests that experienced clinicians can develop the ability to differentiate very early (*coarse*) VF from very late (*fine*) VF. Most experienced clinicians also have a sense of which of these two rhythms is more likely to result in successful defibrillation. Is there a way to quantify these characteristics in waveform and, thus, relate them to the duration of time in VF? The answer may lie in chaos theory and applied fractal geometry.

Chaos Properties of VF. At first glance VF may appear to consist of mere random fluctuation in the electrical waveform. On closer inspection it appears to have chaotic properties, i.e., there is a quantifiable underlying structure to the waveform. Whether chaos is actually present in VF has been the subject of debate in the scientific literature.[33–35] A recent study that analyzed the entire digitized ECG waveform (not just peak-to-peak variability) seems to offer proof that VF does indeed have chaotic properties.[36] In this study analyzing both porcine and human VFs, under varying recording conditions, Sherman et al. demonstrated that a flat, ring-like, two-dimensional attractor could be constructed from VF recordings.[36] Calculation of the correlation and embedding dimensions, as well as Lyapunov and Hurst exponents, supported the premise that the VF waveform possesses chaotic, nonrandom structure. These calculations consis-

tently demonstrate that VF is chaotic rather than random. The scaling exponent is one estimate of the fractal self-similarity dimension of the VF waveform that was shown to correlate closely with the duration of VF, indicating that it might have some clinical utility. Scaling exponent values are low immediately after the onset of VF (mean ± SD 1.18 ± 0.03), gradually increase through the first 5 minutes (1.29 ± 0.06), and begin to plateau at 12–14 minutes of VF (1.75 to 1.89) (Fig. 3). A low scaling exponent value indicates VF of short duration and a high value indicates prolonged VF.

Detailed examination of the scaling exponent showed that this measure not only correlates with the duration of VF, but also is independent of amplitude.[37] This is an extremely important characteristic. Amplitude of the ECG varies greatly from patient to patient, and can be affected by many other variables (type and size of electrode, electrode placement, lead selection, gain, skin resistance, body habitus, etc.). Thus, a quantitative tool for estimating the duration of VF that is independent of recording conditions will have the advantage of not being contaminated by extraneous fluctuations in amplitude. It was also noted that the scaling exponent could be used to differentiate early VF (<4 minutes) from late VF (>4 minutes) (Fig. 3). Others have suggested that 4 minutes of VF is an important treatment marker after which optimal treatment of prolonged VF may differ from the optimal treatment of early VF.

The scaling exponent does seem to be more than just a measure of VF duration. It may be useful in predicting the outcome of defibrillation. In a preliminary study of 75 human AED recordings, the pre-shock value of the scaling exponent predicted the success or failure of the defibrillation.[38] This study demonstrated that lower values of the scaling exponent (indicating early VF) were associated with return of organized electrical activity (ROEA), ROSC, and survival to hospital discharge. Receiver operating characteristic (ROC) curves revealed that the scaling exponent accounted for 0.70 of the area under the curve for predicting ROEA, and an area under the curve of 0.84 for predicting survival to hospital discharge.

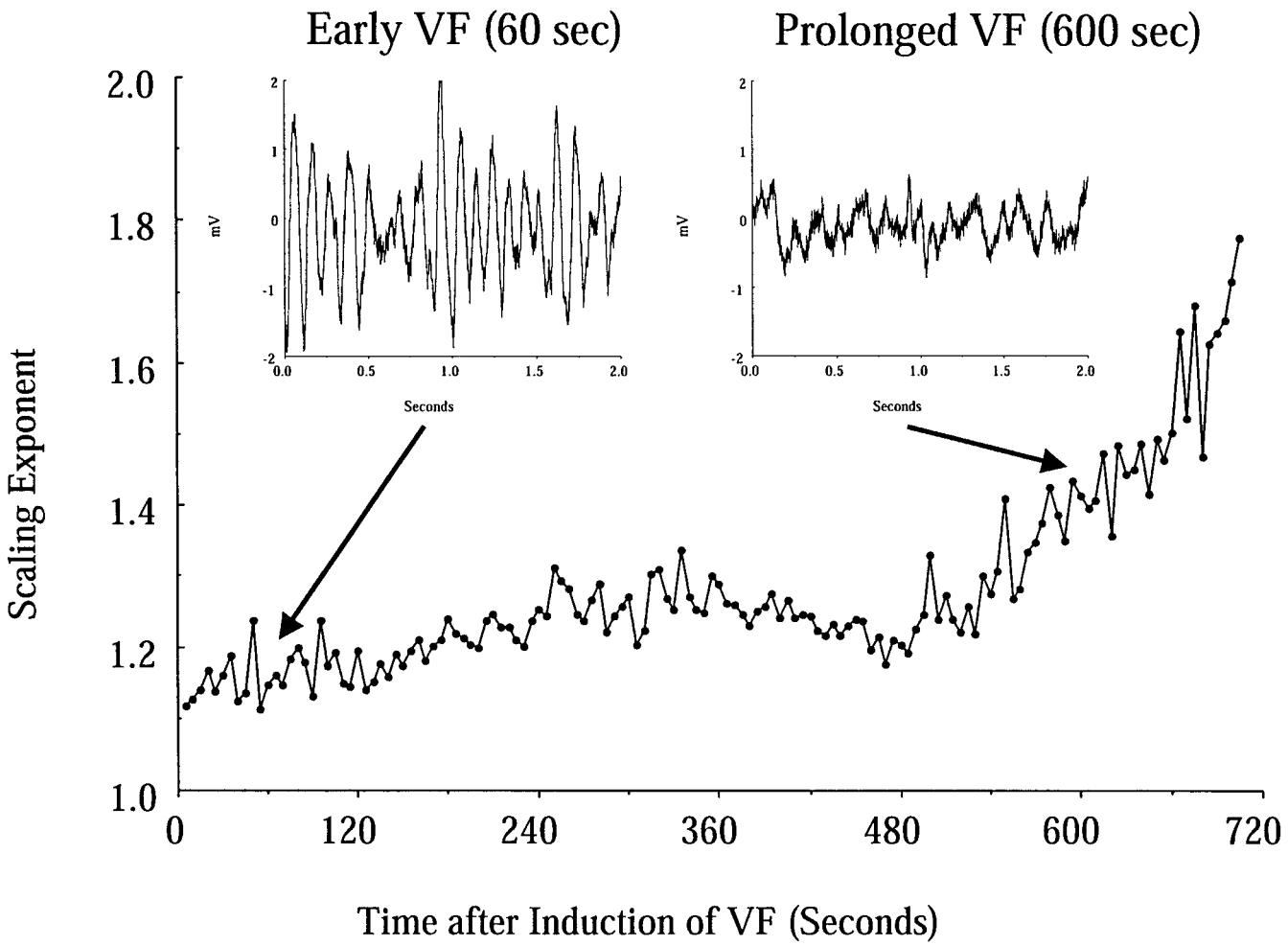

Figure 3. Ventricular fibrillation (VF) waveform morphology changes after prolonged VF in swine. This change can be measured using the scaling exponent, a statistic that is normalized for amplitude and therefore is independent of recording conditions. Quantitative measures allow stratification of subjects into early or late (prolonged) VF.

Potential Clinical Applications. Therefore, we may soon have the ability to use information contained in the ECG signal to guide the use of electrical therapy. For example, it will soon be possible to determine the probability of successful defibrillation in real time using the scaling exponent or other quantitative ECG measures.[39,40] If the probability of defibrillation success is high, then immediate defibrillation would be advised. If the probability of defibrillation success is low, indicating prolonged VF, then other therapies [cardiopulmonary resuscitation (CPR) and drug administration] would be advised prior to defibrillation (with re-evaluation of the scaling exponent after the interventions have had time to take effect). The judicious use of defibrillation could result in a reduction of the number of patients who are shocked out of VF into commonly lethal ECG rhythms (i.e., asystole and PEA). The fact that the initial ECG characteristics may be able to identify patients who will survive to hospital discharge has implications for the entire *chain of survival*. Such real-time measures could potentially allow individualized and titrated therapy rather than purely algorithmic approaches.

Perfusion Prior to Defibrillation for Prolonged VF. Since electrical therapy seems to be the only effective intervention we have to offer patients, the push to make AED technology widely available, i.e., public access defibrillation (PAD), seems well founded.[41] However, a wealth of evidence suggests that defibrillation of *prolonged VF* may harm some patients by converting their ECG rhythms from VF to a more resuscitation-refractory rhythm. A small body of evidence suggests that other interventions prior to the first defibrillation attempt (when VF is prolonged) may improve defibrillation success.

Several basic science investigations provide insight into the possible benefit of delaying defibrillation. The first study was conducted in dogs after 7.5 minutes of VF.[42] This investigation compared immediate defibrillation with the use of high-dose epinephrine (HDE) and 90 seconds of CPR prior to defibrillation. Immediate defibrillation resulted in ROSC in three of 14 (21%) compared with nine of 14 (64%) animals pretreated with HDE and CPR, which improved coronary perfusion prior to defibrillation. A second study done in swine, after 8 minutes of untreated VF, compared immediate defibrillation with the administration of a four-drug cocktail and 2 minutes of CPR before the first shock.[43] This study showed that a drugs/CPR-first approach resulted in a higher rate of ROSC (7/9, 77%) and one-hour survival (4/9, 44%) when compared with defibrillation first (ROSC 2/9, 22%, and one-hour survival 0/9, 0%). A follow-up study by the same investigators compared an expanded cocktail of drugs (that included an antioxidant) and delayed countershock with the ACLS approach.[44] When a combination of drugs and CPR was given over a 2-minute period prior to the first shock, eight of eight (100%) of the animals had ROSC and all (100%) survived to the one-hour endpoint. The group that was shocked first had three of eight (38%) attain ROSC with only one of eight (13%) surviving for one hour.

In one of the most important studies in recent years, Cobb et al. conducted a prospective population-based study in more than 1,100 cases of human out-of-hospital VF.[45] They introduced a 90-second pretreatment therapy of CPR prior to defibrillation in an existing emergency medical technician (EMT) AED program. They observed that pretreatment with 90 seconds of CPR was associated with an increase in the rate of survival to hospital discharge (30%) when compared with immediate defibrillation (24% survival to discharge). The difference in survival rates was even more pronounced when VF was prolonged (more than 4 minutes). These findings in two independent laboratories, in two different higher-order species (canine and swine), coupled with one human study of out-of-hospital VF, are strongly suggestive of the need to explore alternative therapies. The simplified approach for treating all VF (shock–shock–shock) may not be the optimum therapy, especially when VF is prolonged.

If the first defibrillation attempt is to be delayed in patients who are known to have been in prolonged VF, it remains unclear what the best alternative therapy should be. The best choice of drug therapy prior to the first defibrillation attempt in prolonged VF is unclear. Some evidence shows that none of the drugs in the current ACLS armamentarium are associated with improved overall outcome in the treatment of cardiac arrest.[46,47] While epinephrine and, more recently, vasopressin have been recommended to improve flow, human trials of single drug therapies have failed to show significant improvement in survival to hospital discharge.[48–51] It is highly unlikely that there will ever be a single "magic bullet" drug to reverse the complex physiologic cascade triggered by prolonged VF. Thus, the use of perfusion drug cocktails (rather than singular drug treatments) for the treatment of prolonged VF is a critical area for future research.

Perfusion Therapies. Therapy of VF is extremely time-sensitive. In contrast to acute myocardial infarction (AMI), the regional equivalent of cardiac arrest, where the time frame to recover viability is measured in hours, in the global ischemia of cardiac arrest, viability is measured in minutes. No effective pumping action occurs while the heart

ventricle continues to fibrillate. Traditionally we have relied on chest compressions to generate some initial level of flow to facilitate defibrillation after prolonged VF. Reliance solely on chest compression (standard CPR) techniques after prolonged VF is wholly inadequate for reperfusion, as the degree of blood flow generated is so low. Studies of CPR suggest this initial low CPR-generated blood flow further diminishes as the time of cardiac arrest lengthens.[52] Future extra-cardiac circulatory adjuncts, if utilized in a timely manner, could provide this early reperfusion without a total reliance on the ischemic heart. Such adjuncts might include closed chest cardiopulmonary bypass[53,54] and various enhancers of chest compression (i.e., compressible vests that generate circumferential pressure)[55] or adjuncts to improve CPR.[56,57]

Phase II: Reperfusion Injury in Heart and Brain

Only about 20% of cardiac arrest patients with ROSC survive to hospital discharge.[58] Most deaths occur during the first 48 hours of intensive care,[59] mainly due to cardiovascular or neurologic dysfunction. Indeed, the incidence of critical impairment in organ systems other than the heart and brain is relatively low, not high.[60–62] The duration of circulatory arrest is probably the largest determinant of neurologic outcome and severity of reperfusion injury. With reperfusion of the heart and brain, a number of metabolic processes accelerate. Over hours to days these processes may lead to worsening heart and brain injury, culminating with early in-hospital mortality despite the initial successful ROSC.

Heart—Reperfusion. With the re-establishment of blood flow, the function of a number of metabolic and inflammatory pathways are accelerated within the heart. Reperfusion injury is manifested across a wide spectrum of severity, with the most severe injury resulting in stimulation of multiple inflammatory pathways, leading to severe cellular dysfunction, necrosis, and apoptotic cell death. Reperfusion in the heart is initially characterized by a hyperemia due to the hypoxic dilatation of the vasculature. With recovery of reactivity, often the initial hyperemia is followed by a hypoperfused state, and in some areas of the heart a "no reflow" phenomenon may occur. The "no reflow" phenomenon in the microvascular bed is thought to be due to capillary occlusion secondary to platelet/neutrophil occlusion, endothelial cell swelling, and impaired endothelial cell function resulting in reduced nitric oxide release. This has been best characterized in regional myocardial ischemia and reperfusion. Clinical manifestations of reperfusion injury in the heart consist of 1) ventricular arrhythmias and 2) left ventricular (LV) dysfunction.

If cardiac arrest times are relatively short, reperfusion may result in a milder form of reperfusion injury similar to myocardial stunning, which has been best described after regional ischemia.[63] The characteristics of myocardial stunning are reversibility of contractile dysfunction with time and the absence of necrosis. In successfully resuscitated cardiac arrest victims, in the absence of ongoing ischemia (i.e., no coronary occlusion), the post-ischemic LV dysfunction may be reversible. In other cases following ROSC, persistent LV contractile dysfunction may be secondary to ongoing ischemia from a low blood flow state or to myocardial stunning or a combination of both mechanisms.

Heart—Post-ischemic Dysfunction. The underlying mechanisms responsible for myocardial stunning differ some from those of classic reperfusion injury. Whereas most reperfusion injury is mediated by inflammatory injury from endothelial dysfunction and neutrophil activation, nonlethal ischemia with myocardial stunning is thought to be oxidant-mediated rather than inflammatory-mediated.[64] Neutrophils, so prominent in the inflammatory cascades of reperfusion injury, do not appear to play a major role in myocardial stunning, perhaps due to insufficient activation of chemotactic factors, complement, and cellular adhesion molecules.[65,66] Unlike myocardial infarction, the duration of ischemia in the successfully resuscitated cardiac arrest heart is generally initially of insufficient duration to result in myocardial necrosis. Instead, the early LV dysfunction is more likely due to myocardial stunning.

Myocardial Stunning. The two main criteria that define myocardial stunning are 1) abnormal ventricular function despite normal blood flow and 2) the reversibility of myocardial dysfunction.[67] Both of these criteria are absent with myocardial ischemia. The underlying mechanisms thought to be responsible for myocardial stunning are 1) reactive oxygen species (ROS) injury and 2) intracellular calcium overload. Both mechanisms are thought to result in contractile protein dysfunction. The basis for the oxyradicals hypothesis is the burst of ROS generation that occurs with the reintroduction of oxygen to the ischemic tissue. These ROS have an unpaired electron, which makes them highly reactive within the cell and can result in damage to proteins, unsaturated lipids, and DNA. It appears that ROS injury at the cellular level may directly damage the contractile proteins, resulting in contractile protein dysfunction. This tenet is supported by experiments in which cardiac muscle exposed to ROS showed the same contractile dysfunction as seen in stunned myocardium.[68] The

second major hypothesis is transient intracellular calcium overload resulting in decreased responsiveness of the contractile filaments to calcium.[69] Intracellular calcium overload, which occurs with reperfusion, is thought to trigger myofilament dysfunction, leading to excitation contraction uncoupling and decreased myocardial force with each contraction. Most likely myocardial stunning is due to a combination of the two mechanisms.

Post-arrest LV Contractile Dysfunction. Post–cardiac arrest LV dysfunction has been described in animal models. The degree of LV dysfunction increases as the length of ischemic VF increases.[70] Post-resuscitation myocardial dysfunction in a swine model of VF with 4 minutes of global ischemia followed by 8 minutes of CPR and then defibrillation was characterized by reduced contractile function and ventricular dilation.[71] In a swine model of VF cardiac arrest of 10 or 15 minutes, both systolic dysfunction and diastolic dysfunction were noted between two and five hours after initial resuscitation. This dysfunction was characterized by diffuse systolic wall motion abnormalities, decreased ejection fraction, increased end-systolic volume, reduced cardiac output, and decreased tau (a function of isovolumetric relaxation). All of these parameters were improved at 24 hours and returned to normal by 48 hours.[72] This study suggests that if early post-VF dysfunction can be supported and ongoing ischemia prevented, contractile function can recover.

Epinephrine used during resuscitation may exacerbate the post-resuscitation dysfunction. In a rat model of VF cardiac arrest, epinephrine was compared with phenylephrine, epinephrine + esmolol, and placebo. The dP/dt and the survival time were significantly depressed in the post-resuscitation period compared with phenylephrine. This effect was ameliorated in the epinephrine + esmolol group, suggesting beta-1 agonist activity may exacerbate the early post-resuscitation dysfunction.[73] A confounding factor in this study was the significant higher defibrillation requirement in the epinephrine group, which could itself be responsible for increased dysfunction. In a separate study without adrenergic agents, the degree of post-resuscitation dysfunction was directly proportional to the defibrillation energy used.[74] In another study with the same model, both carbon dioxide (CO_2)-generating and CO_2-consuming buffer agents administered during CPR seemed to lessen post-resuscitation myocardial dysfunction.[75] However, a later study by the same group found greater post-resuscitation myocardial dysfunction after administration of buffer in combination with an adrenergic agent as compared with an adrenergic with placebo.[76]

Heart—Potential Reperfusion Therapies

Inotropic Support. In the early post-resuscitation period, if myocardial dysfunction compromises adequate tissue perfusion (including myocardial perfusion), inotropic support may be required. This treatment may be both effective and detrimental. Studies in regional myocardial ischemia models of stunning note myocardial dysfunction can be reversed with epinephrine.[77] In another study of regional ischemia in a swine model, dobutamine effectively improved myocardial function in the stunned myocardium, but at a metabolic price. Creatine phosphate was noted to decrease, and lactate to increase, in the stunned myocardium.[78] Another study in swine noted reversal of dysfunction with dobutamine, with no creatine phosphate overshoot as was seen in control during reperfusion, and adenosine triphosphate (ATP) levels were maintained.[79] In a VF cardiac arrest swine model, dobutamine was shown to reverse early post-resuscitation myocardial dysfunction.[80]

Metabolic Support. With the onset of ischemia, anaerobic metabolism allows for a temporary, albeit reduced, ongoing level of high-energy phosphate synthesis. Eventually glycolysis is inhibited by the accumulation of by-products, reduced nicotinamide adenine dinucleotide (NADH), lactate, and protons.[81] Restoration of normal perfusion (reperfusion) does not necessarily result in the heart's resuming regular metabolic function. Tricarboxylic acid (TCA) cycle function may be depressed secondary to depletion of TCA cycle intermediates. The heart is capable of utilizing different substrates depending on concentration and workload. This is true of the perfused fibrillating heart as well.[82] During reperfusion, the heart preferentially utilizes free fatty acids due to high circulating levels of free fatty acids, as a result of high concentrations of circulating catecholamines. Free fatty acid oxidation inhibits glucose uptake and glucose oxidation (by inhibiting pyruvate dehydrogenase). Free fatty acid oxidation requires higher levels of oxygen consumption that result in oxygen wastage. In addition, free fatty acid metabolites during ischemia are themselves toxic to the myocardium.[83]

Post-ischemic metabolic support for the heart has primarily consisted of increasing myocardial glucose uptake and utilization and repletion of TCA intermediates and amino acids. During ischemia, with some preserved flow allowing for glucose delivery to the myocytes, ATP derived from glycolysis is preferentially used to maintain membrane integrity.[84] With reperfusion, glucose is the preferred substrate of the heart, resulting in better function with less oxygen utilization. Glucose, insulin and potassium (GIK) have been utilized in patients following AMI and cardiac surgery with

TABLE 1. Potential Reperfusion Therapies for the Heart and Brain

Heart*	Brain
Inotropes (dobutamine)	Excitatory amino acid antagonists
Metabolic (GIK, amino acids)	Antioxidants
Antioxidants (SOD, catalase, melatonin, vitamin E)	Hypothermia
K_{ATP} openers (nicorandil, aprikalim)	Blood flow promotion
Na^+/H^+ exchange inhibitors (cariporide)	Growth factors
Ca^{+2} blockers (calpain inhibitors, Ca^{+2} channel blockers)	Caspase or calpain inhibitors

*GIK = glucose, insulin, and potassium; SOD = superoxide dismutase; K_{ATP} = adenosine triphosphate-sensitive potassium; NA^+/H^+= sodium/hydrogen; Ca^{+2} = calcium.

some success. Most of the early AMI studies were inconclusive. However, a recent meta-analysis of randomized, placebo-controlled studies in AMI showed a 28% reduction in early mortality with GIK treatment.[85] A recent multicenter trial, ECLA, noted a significant reduction in early AMI mortality with GIK.[86] However, a second multicenter study failed to show any benefit with GIK following AMI.[87] Further trials are anticipated to resolve this issue. In the post-ischemic heart, insulin increases myocyte glucose uptake by translocation of glucose transporters within the cell membrane, decreases plasma free fatty acid levels, and may directly stimulate pyruvate dehydrogenase, thereby promoting TCA cycle function.[88] Large doses of insulin were noted in animal models to have an inotropic effect.[89] Recently, we noted that GIK administration during reperfusion following global ischemia in the isolated perfused heart improved post-ischemic LV function and recovery of high-energy phosphates.[90,91]

Amino acid replacement has been shown to improve hemodynamic outcome in postoperative hearts.[92] Specifically, postoperative infusions of amino acids, glutamate, and aspartate have shown some benefit. The value of repleting these amino acids is probably due to their role in the malate–aspartate shuttle, which transfers reducing equivalents from NADH in the cytosol to the mitochondria where they are utilized in the electron-transport chain. Another amino acid that may have a role in the reperfusion period is arginine, due to its metabolism to nitric oxide. The value of these metabolic therapies in the setting of early resuscitation from VF cardiac arrest is not known.

Antioxidants. Oxidative stress with formation of ROS is an ongoing process, being a normal by-product of aerobic metabolism. From molecular oxygen, reactive intermediates of superoxide, hydrogen peroxide, and hydroxyl radicals are all formed. All of theses compounds are characterized by an unpaired electron, which makes them highly reactive. Under normal circumstances the cell is able to deal with this oxidative stress through its own intrinsic reducing pathways. These internal antioxidants include glutathione, superoxide dismutase (SOD), and catalase. Glutathione oxidation in cells (including myoctyes) reduces hydrogen peroxide to water. Superoxide dismutase changes superoxide radical to hydrogen peroxide, which is then reduced to water by either glutathione or catalase. Other intracellular ROS-reducing agents (antioxidants) include ascorbate, vitamin E, and beta-carotene. These mechanisms protect the cell unless the increase in ROS overwhelms the cellular defenses as may occur during reperfusion following a period of ischemia. With ischemia reperfusion, there is a burst of ROS, which overwhelms the cellular defenses and results in cellular injury.

A number of studies have investigated the use of antioxidants to ameliorate ROS injury during early reperfusion of the myocardium. In earlier experiments using regional ischemia models, antioxidant therapy consisting of SOD and catalase was shown to improve regional contractile function after 15 minutes of occlusion and three hours of reperfusion.[93–95] This constituted indirect evidence that ROS were associated with reperfusion myocardial injury. Later studies provided more direct evidence for the role of ROS-mediated reperfusion injury. Using a spin trap analysis, alpha-phenyl N-tert-butyl nitrone (PBN), and electron spin resonance in the anesthetized open-chest dog model, Bolli et al. noted free radical production was proportional to the intensity of ischemia before reperfusion and was markedly decreased with SOD and catalase.[96] They noted improved post-ischemic systolic wall thickening with antioxidant therapy. This finding was confirmed in the conscious, nonanesthetized dog model, where a burst of ROS was noted at the time of reperfusion after 15 minutes of regional ischemia and peaked at 1–2 minutes after reperfusion. Antioxidants attenuated this ROS burst and improved wall function following reperfusion.[97]

Antioxidant therapy for cardiac arrest has been investigated in cardiac arrest models as part of a broader "reperfusion cocktail" therapy.[44,98] However, it is difficult to isolate the role of antioxidants independent of the other cocktail components in these studies. In models of ischemia–reperfusion, other ROS scavengers have shown amelioration of

reperfusion injury and myocardial stunning. Melatonin, a hydroxyl radical scavenger, was noted to improve recovery of post-ischemic LV function.[99] Vitamin E was noted to scavenge peroxyl radicals and reduce the incidence of VF with reperfusion.[100] Alpha-tocopherol analogs have inhibited lipoperoxide production and decreased incidence of reperfusion arrhythmias.[101]

In summary, antioxidant therapies have been shown, in numerous basic science and animal studies of myocardial ischemia and reperfusion, to ameliorate ROS production and improve post-ischemic contractile dysfunction. This is, however, less well studied in models of cardiac arrest. A primary obstacle to antioxidant therapy in cardiac arrest is the need to administer the antioxidant prior to reperfusion so as to be in the tissues during early reperfusion. Studies indicate they are most effective when given pre-ischemia.

K_{ATP} Channel Openers. K_{ATP} channels were first described in ventricular myocytes by Noma.[102] During ischemia, these channels open, allowing the egress of intracellular potassium to the extracellular space. Physiologic concentrations of ATP inhibit channel opening and thus these channels were initially termed "ATP-dependent potassium channels." Subsequently, a number of other modulators of the K_{ATP} channels have been noted. These include pH, fatty acids, nitric oxide, SH-redox state, G-proteins, and various ligands, including adenosine. As a result, these K_{ATP} channels are now termed "ATP-sensitive potassium channels."

An important role of these channels in ischemia and reperfusion has recently been elucidated. K_{ATP} channel opening seems to be the mediator of ischemic preconditioning. Administration of K_{ATP} channel blockers completely abolishes preconditioning. Adenosine A1 receptor activates K_{ATP} channel opening, and conversely administration of adenosine A1 blockers extinguishes preconditioning, suggesting a common signaling pathway. Current thoughts are that adenosine A1 receptor activation mobilizes protein kinase C (PKC), which in turn activates K_{ATP} channel opening. Blocking these channels abolishes the ischemic pre-conditioning response.[103] More recent evidence suggests that it is not the sarcolemmal K_{ATP} channels that mediate cardioprotection, but instead the mitochondrial K_{ATP} channels.[104]

This mechanism seems to be important in myocardial stunning as well. Utilization of a K_{ATP} channel opener, aprikalim, in a canine model of 15-minute coronary artery occlusion followed by reperfusion was noted to improve post-ischemic contractile dysfunction (myocardial stunning).[105] A number of agents, including nicorandil, pinacidil, cromakalim, and aprikalim, have been shown in multiple species of ischemic reperfusion models to improve post-ischemic LV function, to conserve ATP during ischemia, to enhance ATP regeneration during reperfusion, and to decrease myocardial infarct size.[106,107] These agents appear to be most effective when given before the onset of ischemia. The effect of these agents given during reperfusion only is very weak, suggesting much of their benefit may occur during ischemia.[108] Another potential obstacle to their use in clinical models of ischemia and reperfusion is their significant vasodilatory activity leading to profound hypotension. This hypotension has been circumvented in models where K_{ATP} channel openers were given intracoronary.[109] While these agents have not been specifically investigated in cardiac arrest, they may be of potential benefit in cardiac arrest if they could be administered during ischemia prior to reperfusion.

Na^+/H^+ Exchange (NHE). With reperfusion of the ischemic heart, preservation of the intracellular acidosis has been shown to improve post-ischemic function.[110] It is thought that the rise in intracellular pH early in reperfusion makes the myofilaments vulnerable to injury. Other studies have shown that reduction of the intracellular calcium (Ca^{+2}) overload, which occurs at the time of reperfusion, improves post-ischemic myocardial function. The sodium/calcium (Na^+/Ca^{+2}) exchanger in the cell is responsible for the intracellular Ca^{+2} overload, which occurs at the time of reperfusion. During ischemia, the sodium/hydrogen (Na^+/H^+) exchanger is stimulated as H ions accumulate within the ischemic cell.[111] The Na^+/Ca^{+2} exchanger is stimulated during reperfusion by the increased intracellular Na^+ concentrations, which result in large part from the stimulation of the Na^+/H^+ exchanger by the decreasing intracellular pH during ischemia. As a result, H^+ is pumped out of the cell and Na^+ is pumped in. With reperfusion, the Na^+/Ca^{+2} exchanger is activated, and Ca^{+2} is pumped into the cell in exchange for the electro-neutral Na^+, which is pumped out. The result is intracellular Ca^{+2} overload.[112]

A number of recent studies have focused on specific blockers of the Na^+/H^+ exchange. Isolated perfused rat hearts treated with cariporide, a specific NHE blocker, had lower $[Ca^{+2}]_i$ (intracellular) and prolonged lower pH_i during early reperfusion compared with control hearts.[113] In another study, isolated guinea pig hearts treated with cariporide had improved post-ischemic function, higher creatine phosphate levels during reperfusion, and decreased $[Na^+]_i$ during ischemia.[114] In both of theses studies, cariporide was given pre-ischemia, which limits its clinical utilization in reperfusion of cardiac arrest. Currently, cariporide is undergoing

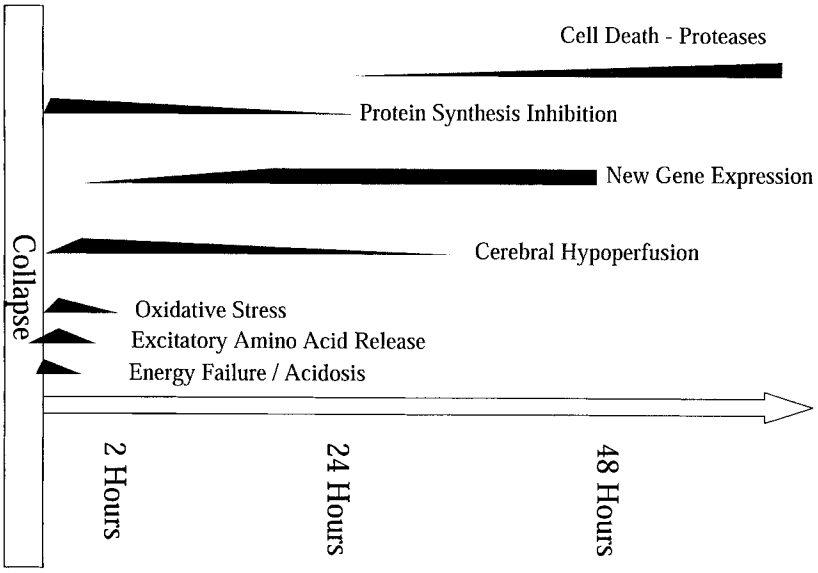

Figure 4. Multiple mechanisms of injury are active at different times during brain reperfusion. Interventions targeting events during ischemia and early reperfusion (such as free radicals) will have less efficacy if delayed, whereas interventions that target later events (such as altered gene expression) may have longer therapeutic windows.

clinical trials in acute myocardial infarction patients.[115–117]

Calcium Blockers. Calcium channel blockers have been known to lessen the effects of myocardial ischemia.[118,119] Calcium channel blockers have also been effective in various models of ischemia and reperfusion in diminishing the degree of myocardial stunning.[120,121] This effect, however, may be primarily mediated by the effects during ischemia rather than at the time of reperfusion. Presumably by modifying the ischemic insult, one indirectly ameliorates the reperfusion injury, as the duration and extent of ischemia determine the severity of the injury induced by reperfusion. Calcium channel blockers seem to be of limited value when given after reperfusion. Calcium channel blockers may also be effective as ROS scavengers during ischemia and reperfusion.[122]

Various studies suggest that Ca^{+2} availability within the cell is not diminished in stunned myocardium. Instead, the contractile response to calcium appears to be diminished. Immunohistochemistry studies suggest that the underlying problem is diminished myofilament responsiveness to calcium.[123,124] Contractile dysfunction is due to damage to the contractile proteins, which occurs at the time of reperfusion, but was not seen during ischemia.[125] Some investigators have postulated that this injury to contractile proteins is the result of calcium-activated proteases, such as calpain I.[69] The calcium overload, which occurs in reperfused myocytes, is sufficient to activate calcium-activated proteases known as calpains. Calpains are present in many tissues, including the myocardium. Support for calpain-induced contractile dysfunction is found in studies that show exposure of the myofilaments to calpain I reproduces the same type of myofilament dysfunction without ischemia. This dysfunction is reversed or prevented by coincubation of the myofilaments with calpastin, a calpain inhibitor.[125] Use of calpain inhibitors in models of ischemia and reperfusion has shown improved function in isolated perfused hearts.[126,127]

Brain—Reperfusion. Many of the metabolic changes observed in the reperfused heart are also present in the reperfused brain. Analogous to postischemic myocardial dysfunction, a period of global brain dysfunction clinically manifest as coma often follows global brain ischemia, even when ultimate neurologic recovery is favorable. The biochemical complexities of reperfusion brain injury have recently been reviewed[126] and are beyond the scope of this paper. However, a brief overview of mechanisms that are potential targets for therapy during and after resuscitation can highlight implications for treatment of patients with prolonged cardiac arrest (Fig. 4).

Brain Reperfusion. Several triggers of neuronal death are present during ischemia and immediately after reperfusion of the ischemic brain: energy failure, excitatory amino acid release, and free radical generation. However, these changes appear to be transient. High-energy phosphates return to near normal levels within 20 minutes of reperfusion.[127] Likewise, elevated excitatory amino

acid levels return to near normal levels within 30–60 minutes.[128] Finally, oxidative stress detected by depletion of cellular antioxidants occurs immediately after reperfusion and recovers within two hours.[129]

During the subacute phase of brain reperfusion, regional and global cerebral hypoperfusion can be accompanied by altered gene expression. Cerebral hypoperfusion occurs both regionally and globally after reperfusion[130,131] and can result in secondary brain injury. During the same interval of reperfusion, increased activation of several specific transcription factors is observed.[132] Consequently, particular genes are expressed at increased levels after global ischemia,[133] including both gene products associated with programmed cell death[134–136] and those associated with neuronal survival.[137] Finally, neuronal death occurs over hours and days after reperfusion, and is associated with increases in certain cell death effectors. These effectors include Bax protein expression,[134,135] enzyme release from mitochondria,[138] caspase activation,[136] and DNA cleavage.[139]

Therapeutic Interventions. Two earlier multicenter studies specifically tested the use of thiopental and a calcium channel blocker, lidoflazine, in clinical cardiac arrest. Both trials were designed to evaluate the best neurologic recovery achieved at six months following administration of pentobarbital[140] and lidoflazine[141] soon after ROSC. In both studies, the study drug was administered early after ROSC in comatose cardiac arrest survivors. There was no difference in six-month survival or in best neurologic recovery achieved with either treatment.

In preclinical studies, drugs targeted at specific mechanisms of brain injury, including excitatory amino acid antagonists,[142,143] free radical scavengers,[144] and reduced oxygen tension,[145] have failed to produce any dramatic improvement in neurologic outcome. Treatment after reperfusion already may be too late to alter outcome. Recently caspase inhibtors have shown equivocal effects on ischemic neuronal injury.[146,147] Perhaps by the time these effectors of cell death are activated, neuronal injury has progressed too far to allow functional recovery.

Less specific physical manipulations have shown more robust improvement. Induction of mild hypothermia, for example, can dramatically improve neuronal survival after cerebral arterial occlusion or cardiac arrest.[148–150] In contrast to drugs, this type of physical manipulation can interfere with many of the early triggers of brain injury[151,152] as well as intracellular signaling pathways controlling gene expression.[153] Similarly, controlled hypertension and optimal blood rheology can mitigate regional cerebral hypoperfusion.[154] Clinical trials of induced hypothermia are ongoing.[155]

CONCLUSIONS

Taken together, these data illustrate that the brain, like the heart, suffers a period of depressed function after cardiac arrest during which the molecular manifestations of injury continue to unfold. Reversal of the no-flow state after prolonged VF must occur in minutes in order to both obtain ROSC (phase I resuscitation) and limit heart and brain dysfunction following ROSC (phase II resuscitation). Although initial cardiac arrest resuscitation (phase I) must occur within minutes, the injury and dysfunction associated with reperfusion may persist for hours to days. Different tailored therapies may be needed for phase I and phase II resuscitation. With improved understanding of the complex pathways involved in ischemia and reperfusion in the heart and brain, a cocktail combination of therapies will probably be needed. This post-resuscitation dysfunctional period is another window of therapeutic opportunity that may be used to decrease the high post–cardiac arrest morbidity and mortality.

References

1. Becker LB. The epidemiology of sudden death. In: Paradis NA, Halperin H, Nowak R (eds). Cardiac Arrest: The Science and Practice of Resuscitation Medicine. Baltimore, MD: Williams & Wilkins, 1996.
2. Eisenberg MS, Horwood BT, Cummins RO, et al. Cardiac arrest and resuscitation: a tale of 29 cities. Ann Emerg Med. 1990; 19:179–86.
3. Larsen MP, Eisenberg MS, Cummins RO, Hallstrom AP. Predicting survival from out-of-hospital cardiac arrest: a graphic model. Ann Emerg Med. 1993; 22:1652–8.
4. Emergency Cardiac Care and Committee and Subcommittees, American Heart Association. Guidelines for cardiopulmonary resuscitation. Part 6: Advanced Cardiovascular Life Support, Section 2: Defibrillation. Resuscitation. 2000; 46:109–13.
5. Kerber RE, Grayzel J, Hoyt R, Marcus M, Kennedy J. Transthoracic resistance in human defibrillation: influence of body weight, chest size, serial shocks, paddle size and paddle contact pressure. Circulation. 1981; 63:676–82.
6. Sirna SJ, Ferguson DW, Charbonnier F, Kerber RE. Factors affecting transthoracic impedance during electrical cardioversion. Am J Cardiol. 1988; 62:1048–52.
7. Dahl CF, Ewy GA, Ewy MD, Thomas ED. Transthoracic impedance to direct current discharge: effect of repeated countershocks. Med Instrum. 1976; 10:151–4.
8. Hargarten KM, Steuven HA, Waite EM, et al. Prehospital experience with defibrillation of coarse ventricular fibrillation: a ten year review. Ann Emerg Med. 1990; 19:157–62.
9. DiCola VC, Freedman GS, Downing SE, Zaret L. Myocardial uptake of technetium-99m stannous pyrophosphate following direct current transthoracic countershock. Circulation. 1976; 54:980–6.
10. Doherty PW, McLaughlin PR, Billingham M, Hernoff R, Goris ML, Harrison DC. Cardiac damage produced by direct current countershock applied to the heart. Am J Cardiol. 1979; 43:225–32.
11. Ehsani A, Eqy GA, Sobel BE. Effects of electrical countershock on serum creatine phosphokinase (CPK) isoenzyme ac-

tivity. Am J Cardiol. 1976; 37:12–8.
12. Trouton PG, Allen JD, Young LK, Rooney JJ, Adgey AAJ. Metabolic changes and mitochondrial disfunction early following transthoracic countershocks in dogs. PACE. 1989; 12: 1827–34.
13. Warner ED, Dahl C, Eqy GA. Myocardial injury from transthoracic defibrillator countershock. Arch Pathol. 1975; 99: 55–63.
14. Wilson CM, Allen JD, Bridges JB, Adgey AAJ. Death and damage caused by multiple direct current shocks: studies in animal model. Eur Heart J. 1989; 10:528–36.
15. Cates AW, Wolf PD, Hillsley RE, Souza JJ, Smith WM, Ideker RE: The probability of defibrillation success and the incidence of postshock arrhythmia as a function of shock strength. PACE. 1994; 17:1208–17.
16. Schuder JC, Gold JH, Stoeckle H, McDaniel WC, Cheung KN. Transthoracic ventricular defibrillation in the 100kg calf with symmetrical one-cycle bi-directional rectangular wave stimuli. IEEE Trans Biomed Eng. 1983; 30:415–22.
17. Jones JL, Jones RE, Balasky G. Improved cardiac cell excitation with symmetrical biphasic defibrillator waveforms. Am J Physiol. 1987; 253:H1418–H1424.
18. Chapman PD, Vetter JW, Souza JJ, Wetherbee JN, Troup PJ. Comparison of monophasic with single and dual capacitator biphasic waveforms for nonthoracotomy canine internal fibrillation. J Am Coll Cardiol. 1989; 14:242–5.
19. Gliner BE, Lyster TE, Dillion SM, Bardy GH. Transthoracic defibrillation of swine with monophasic and biphasic waveforms. Circulation. 1995; 92:1634–43.
20. Wyse DG, Kavanagh KM, Gillis AM, et al. Comparison of biphasic and monophasic shocks for defibrillation using a nonthoracotomy system. Am J Cardiol. 1993; 71:197–202.
21. Winkle AW, Mead RH, Ruder MA, et al. Improved low-energy defibrillation efficacy in man with the use of a biphasic truncated exponential waveform. Am Heart J. 1989; 117: 122–7.
22. Bardy GH, Ivey TD, Allen MD, Johnson G, Mehra R, Greene HL. A prospective randomized evaluation of biphasic versus monophasic waveform pulses on defibrillation efficacy in humans. J Am Coll Cardiol. 1989; 14:728–33.
23. Greene HL, Dimarco JP, Kudenchuck PJ, et al. Comparison of monophasic and biphasic defibrillating pulse waveforms for thransthoracic cardioversion. Am J Cardiol. 1995; 75:1135–8.
24. Swartz JF, Fletcher RD, Karasik PE. Optimization of biphasic waveforms for human nonthoracotomy defibrillation. Circulation. 1993; 88:2646–54.
25. Jones JL, Milne KB. Dysfunction and safety factor strength–duration curves for biphasic defibrillator waveforms. Am J Physiol. 1994; 266:H263–H271.
26. Osswald S, Trouton TG, O'Nunain SS, Holden HB, Ruskin JN, Garan H. Relation between shock-related myocardial injury and defibrillation efficacy of monophasic and biphasic shocks in a canine model. Circulation. 1994; 90:2501–9.
27. Reddy RK, Gleva MJ, Gliner BE. Biphasic transthoracic defibrillation causes fewer ECG ST-segment changes after shock. Ann Emerg Med. 1997; 30:127–34.
28. Bardy GH, Marchlinski FE, Sharma AD, et al. Multicenter comparison of truncated biphasic shocks and standard damped sine wave monophasic shocks for transthoracic ventricular defibrillation. Circulation. 1996; 94:2507–14.
29. Scheatzle MD, Menegazzi JJ, Allen TL, Durham SB. Evalutaion of biphasic transthoracic defibrillation in an animal model of prolonged ventricular fibrillation. Acad Emerg Med. 1999; 6:880–6.
30. Niemann JT, Burian D, Garner D, Lewis RJ. Monophasic versus biphasic transthoracic countershock after prolonged ventricular fibrillation in a swine model. J Am Coll Cardiol. 2000; 36:932–8.
31. Poole JE, White RD, Kanz KG. Low-energy impedance-compensating biphasic waveforms terminate ventricular fibrillation at high rates in victims of out-of-hospital cardiac arrest. J Cardiovasc Electrophysiol. 1997; 8:1373–85.
32. Higgins SL, Herre JM, Epstein AE, et al. A comparison of biphasic and monophasic shocks for external defibrillation. Prehosp Emerg Care. 2000; 4:305–13.
33. Kaplan DT, Cohen RJ. Is fibrillation chaos? Circ Res. 1990; 67:886–92.
34. Gray RA, Pertsov AM, Jalife J. Spatial and temporal organization during cardiac fibrillation. Nature. 1998; 392:20–1.
35. Witkowski FX, Leon LJ, Penkoske PA, et al. Spatiotemporal evolution of ventricular fibrillation. Nature. 1998; 392: 78–82.
36. Sherman LD, Callaway CW, Menegazzi JJ. Ventricular fibrillation exhibits dynamical properties and self-similarity. Resuscitation. 2000; 47:163–73.
37. Callaway CW, Sherman LD, Menegazzi JJ, Scheatzle MD. Scaling structure of electrocardiographic waveform during prolonged ventricular fibrillation in swine. Pacing Clin Electrophysiol. 2000; 2:180–91.
38. Callaway CW, Sherman LD, Mosesso VN, Dietrich TJ, Holt E, Clarkson MC. Scaling exponent predicts defibrillation success for out-of-hospital ventricular fibrillation cardiac arrest. Circulation. 2001; 103:1656–61.
39. Watson JN, Addison PS, Clegg GR, Holzer M, Sterz F, Robertson CE. A novel wavelet transform based analysis reveals hidden structure in ventricular fibrillation. Resuscitation. 2000; 43:121–7.
40. Eftestøl, T, Sunde K, Aase SO, Husøy JH, Steenb PA. "Probability of successful defibrillation" as a monitor during CPR in out-of-hospital cardiac arrested patients. Resuscitation. 2001; 48:245–54.
41. Automatic External Defibrillation Task Force, Weisfeldt ML, Kerber RE, McGoldrick RP, et al. American Heart Association report on the Public Access Defibrillation Conference December 8–10, 1994. Circulation. 1995; 92:2740–7.
42. Niemann JT, Cairns CB, Sharma J, Lewis RJ. Treatment of prolonged ventricular fibrillation, immediate countershock versus high-dose epinephrine and CPR preceding countershock. Circulation. 1992; 85:281–7.
43. Menegazzi JJ, Davis EA, Yealy DM, et al. An experimental algorithm versus standard Advanced Cardiac Life Support in a swine model of out-of-hospital cardiac arrest. Ann Emerg Med. 1993; 22:235–9.
44. Menegazzi JJ, Seaberg DC, Yealy DM, Davis EA, MacLeod BA. Combination pharmacotherapy with delayed countershock vs standard Advanced Cardiac Life Support after prolonged ventricular fibrillation. Prehosp Emerg Care. 2000; 4:31–7.
45. Cobb LA, Fahrenbruch CE, Walsh TR, et al. Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation. JAMA. 1999; 281:1182–8.
46. Van Walraven C, Stiell IG, Wells GA, Hebert PC, Vandemheen K, the OTAC Study Group. Do Advanced Cardiac Life Support drugs increase resuscitation rates from in-hospital cardiac arrest? Ann Emerg Med. 1998; 32:544–53.
47. Steill IG, Wells GA, Hebert PC, Laupacis A, Weitzman BN. Association of drug therapy with survival in cardiac arrest-limited role of Advanced Cardiac Life Support drugs. Acad Emerg Med. 1995; 2:264–73.
48. Brown CG, Martin DR, Pepe PE, et al. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. N Engl J Med. 1992; 327:1051–5.
49. Steill IG, Hebert PC, Weitzman BN, et al. High-dose epinephrine in adult cardiac arrest. N Engl J Med. 1992; 327: 1045–50.
50. Abramson NS, Safar P, Sutton-Tyrell K, Craig MT, for the BRCT III Study Group. A randomized clinical trial of escalating doses of high dose epinephrine during cardiac resuscitation [abstract]. Crit Care Med. 1995; 23:A178.
51. Gueugniaud P-V, Mols P, Goldstein P, et al. A comparison of repeated high doses of epinephrine for cardiac arrest outside the hospital. N Engl J Med. 1998; 339:1595–601.
52. Lee SK, Vaagenes P, Safar P, Effect of cardiac arrest time on cortical cerebral blood flow during subsequent standard external cardiopulmonary resuscitation in rabbits. Resuscitation. 1989; 17:105–17.
53. Nagao K, Hayashi N, Kanmatsuse K, et al. Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. J Am Coll Cardiol. 2000; 36:776–83.
54. Reich H, Angelos M, Safar P, Sterz F, Lenov Y. Cardiac resuscitability with cardiopulmonary bypass after increasing fibrillation time in dogs. Ann Emerg Med. 1990; 19:887–90.

55. Halperin HR, Tsitlik JE, Gelfand M, et al. A preliminary study of cardiopulmonary resuscitation by circumferential compression of the chest with use of a pneumatic vest. N Engl J Med. 1993; 329:762–8.
56. Tang W, Weil MH, Schock RB, et al. Phased chest and abdominal compression–decompression. A new option for cardiopulmonary resuscitation. Circulation. 1997; 95:1335–40.
57. Babbs CF. Efficacy of interposed abdominal compression–cardiopulmonary resuscitation (CPR), active compression and decompression-CPR and Lifestick CPR: basic physiology in a spreadsheet model. Crit Care Med. 2000; 28(11 suppl):N199–N202.
58. Callaway CW. Improving neurologic outcomes after out-of-hospital cardiac arrest. Prehosp Emerg Care. 1997; 1:45–54.
59. De Vos R, De Haes HCJM, Koster RW, De Haan RJ. Quality of survival after cardiopulmonary resuscitation. Arch Intern Med. 1999; 159:249–54.
60. Bjork RJ, Snyder BD, Campion BC, Lowenson RB. Medical complications of cardiopulmonary arrest. Arch Intern Med. 1982; 142:500–3.
61. Gaussorgues P, Gueugniaud PY, Vedrine JM, Salord F, Mercatteelo A, Robert D. Bacteremia following cardiac arrest and cardiopulmonary resuscitation. Intens Care Med. 1988; 14: 575–7.
62. Mattana J, Singhala PC. Prevalence and determinants of acute renal failure following cardiopulmonary resuscitation. Arch Intern Med. 1993; 153:235–9.
63. Braunwald E, Kloner RA: The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation. 1982; 66:1146–9.
64. Entman ML, Smith CW. Postreperfusion inflammation: a model for reaction to injury in cardiovascular disease. Cardiovasc Res. 1994; 28:1301–11.
65. Juneau CF, Ito BR, del Balzo U, Engler RL. Severe neutrophil depletion by leukocyte filters or cytotoxic drug does not improve recovery of contractile function in stunned porcine myocardium. Cardiovasc Res. 1993; 27:720–7.
66. Bolli RL. Role of neutrophils in myocardial stunning after brief ischaemia: the end of a six year old controversy (1987–1993). Cardiovasc Res. 1993; 27:728–30.
67. Bolli R. Mechanism of myocardial "stunning." Circulation. 1990; 82:723–8.
68. Gao WD, Liu Y, Marban E. Selective effects of oxygen free radicals on excitation–contraction coupling in ventricular muscle. Circulation. 1996; 94:2597–604.
69. Bolli R, Marban E. Molecular and cellular mechanisms of myocardial stunning. Physiol Rev. 1999; 79:609–34.
70. Tang W, Weil MH, Sun S, Gazmuri RJ, Bisera J. Progressive myocardial dysfunction after cardiac resuscitation. Crit Care Med. 1993; 21:1046–50.
71. Gazmuri RJ, Weil MH, Bisera J, Tang W, Fukui M, McKee D. Myocardial dysfunction after successful resuscitation from cardiac arrest. Crit Care Med. 1996; 24:992–1000.
72. Kern KB, Hilwig RW, Rhee KH, Berg RA. Myocardial dysfunction after resuscitation from cardiac arrest: an example of global myocardial stunning. J Am Coll Cardiol. 1996; 28:232–40.
73. Tang W, Weil MH, Sun S, Noc M, Yang L, Gazmuri RJ. Epinephrine increases the severity of postresuscitation myocardial dysfunction. Circulation. 1995; 92:3089–93.
74. Xie J, Weil MH, Sun S, et al. High-energy defibrillation increases the severity of postresuscitation myocardial dysfunction. Circulation. 1997; 96:683–8.
75. Sun S, Weil MH, Tang W, Fukui M. Effects of buffer agents on postresuscitation myocardial dysfunction. Crit Care Med. 1996; 24:2035–41.
76. Sun S, Weil MH, Tang W, Povoas HP, Mason E. Combined effects of buffer and adrenergic agents on postresuscitation myocardial function. J Pharmacol Exp Ther. 1999; 291:773–7.
77. Becker LC, Levine JH, DiPaula AF, Guarnieri T, Aversano T. Reversal of dysfunction in postischemic stunned myocardium by epinephrine and postextrasystolic potentiation. J Am Coll Cardiol. 1986; 7:580–9.
78. Schulz R, Guth BD, Pieper K, Marin C, Heusch G. Recruitment of an inotropic reserve in moderately ischemic myocardium at the expense of metabolic recovery. Circ Res. 1992; 70:1282–95.
79. Kida M, Fujiwara H, Uegaito T, et al. Dobutamine prevents both myocardial stunning an phosphocreatine overshoot without affecting ATP level. J Mol Cell Cardiol. 1993; 25:875–85.
80. Kern KB, Hilwig RW, Berg RA, et al. Postresuscitation left ventricular systolic and diastolic dysfunction. Treatment with dobutamine. Circulation. 1997; 95:2610–3.
81. Stanley WC, Lopaschuk GD, Hall JL, McCormack JG. Regulation of myocardial carbohydrate metabolism under normal and ischemic conditions. Potential for pharmacological interventions. Cardiovasc Res. 1997; 33:243–57.
82. Angelos MG, Torres CAA, Rath DP, Zhu H, Beckley PD, Robitaille PML. In vivo myocardial substrate alteration during perfused ventricular fibrillation. Acad Emerg Med. 1999; 6: 581–7.
83. Opie LH. Fuels: aerobic and anaerobic metabolism. In: The Heart Physiology, from Cell to Circulation, 3rd Edition. Philadelphia: Lippincott–Raven, 1998.
84. Weiss JN, Lamp ST. Glycolysis preferentially inhibits ATP-sensitive K^+ channels in isolated guinea pig cardiac myocytes. Science. 1987; 238:67–9.
85. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. Circulation. 1997; 96:1152–6.
86. Diaz R, Paolasso EA, Piegas LS, et al. Metabolic modulation of acute myocardial infarction: the ECLA glucose-insulin-potassium pilot trial. Circulation. 1998; 98:2227–34.
87. Ceremuzynski L, Budaj A, Czepiel A, et al. Low-dose glucose-insulin-potassium is ineffective in acute myocardial infarction: results of a randomized multicenter Pol-GIK trial. Cardiovasc Drugs Ther. 1999; 13:191–200.
88. Zaninetti D, Greco-Perotto R, Assimacopoulos-Jeannet F, Jeanrenaud B. Effects of insulin on glucose transport and glucose transporters in rat heart. Biochem J. 1988; 250:277–283.
89. Lucchesi BR, Median M, Kniffen FJ. The positive inotropic action of insulin in the canine heart. Eur J Pharmacol. 1972; 18:107–15.
90. Angelos MG, Murray HN. Glucose-insulin-potassium (GIK) improves left ventricular function after global ischemia in the perfused rat heart [abstract]. Acad Emerg Med. 1999; 6: 512.
91. Angelos MG, Murray HN, Gorsline RT. Glucose, insulin and potassium (GIK) improves myocardial bioenergetic recovery following global ischemia [abstract]. Circulation 1999; 100(suppl I):I-664.
92. Svedjeholm R, Hakanson E, Szabo Z. Metabolic intervention for the ischemic and post-ischemic heart. Wien Klin Wochenschr. 1999; 111:501–11.
93. Myers ML, Bolli R, Lekich RF, Hartley CJ, Roberts RL. Enhancement of recovery of myocardial function by oxygen free-radical scavengers after reversible regional ischemia. Circulation. 1985; 72:915–21.
94. Gross GJ, Farber NE, Hardman HF, Warltier DC. Beneficial actions of superoxide dismutase and catalase in stunned myocardium of dogs. Am J Physiol. 1986; 250:H372-H377.
95. Przyklenk K, Kloner RA. Superoxide dismutase plus catalase improve contractile function in the canine model of the "stunned" myocardium. Circ Res. 1986; 58:148–56.
96. Bolli R, Patel BS, Jeroudi MO, Lai EK, McCay PB. Demonstration of free radical generation in "stunned" myocardium of intact dogs with the use of the spin trap α-phenyl-N-tert-butyl nitrone. J Clin Invest. 1988; 82:476–85.
97. Li XY, McCay PB, Zughaib M, Jeroudi MO, Triana JF, Bolli R. Demonstration of free radical generation in the "stunned" myocardium in the conscious dog and identification of major differences between conscious an open-chest dogs. J Clin Invest. 1993: 92:1025–41.
98. Cerchiari EL, Sclabassi RJ, Safar P, Hoel TM. Effects of combined superoxide dismutase and deferoxamine on recovery of brainstem auditory evoked potentials and EEG after asphyxial cardiac arrest in dogs. Resuscitation. 1990; 19:25–40.
99. Kaneko S, Okumura K, Numaguchi Y, et al. Melatonin scavenges hydroxyl radical and protects isolated rat hearts from ischemic reperfusion injury. Life Sci. 2000; 67:101–12.
100. Walker MK, Vergely C, Lecour S, Adabie C, Maupoil V, Rochette L. Vitamin E analogues reduce the incidence of ven-

tricular fibrillations and scavenge free radicals. Fundam Clin Pharm. 1998; 12:164–72.
101. Abadie C, Ben Baouali A, Maupoil V, Rochette L. An alpha-tocopherol analogue with antioxidant activity improves myocardial function during ischemia reperfusion in isolated working rat hearts. Free Radic Biol Med. 1993; 15:209–15.
102. Noma A. ATP-regulated K^+ channels in cardiac muscle. Nature. 1983; 305:147–8.
103. Gross GJ, Garlid KD. ATP-sensitive potassium channels: a review of their cardioprotective pharmacology. J Mol Cell Cardiol. 2000; 32:677–95.
104. Lui Y, Sato T, O'Rourke B, Marban E. Mitochondrial ATP-dependent potassium channels: novel effectors of cardioprotection? Circulation. 1998; 97:2463–9.
105. Auchampach JA, Maruyama M, Cavero I, Gross GJ. Pharmacological evidence for a role of ATP-dependent potassium channels in myocardial stunning. Circulation. 1992; 86: 311–9.
106. Grover G, Newburger J, Sleph P, et al. Cardioprotective effects of the potassium channel opener cromakalim: stereoselectivity and effects on myocardial adenine nucleotides. J Pharmacol Exp Ther. 1991; 257:156–72.
107. McPherson C, Pierce G, Cole W. Ischemic cardioprotection by ATP-sensitive K^+ channels involves high-energy phosphate preservation. Am J Physiol. 1993; 265:H1809–H1818.
108. Grover GJ, Garlid KD. ATP-sensitive potassium channels: a review of their cardioprotective pharmacology. J Mol Cell Cardiol. 2000; 32:677–95.
109. D'Alonzo A, Darbenzio R, Rarham C, Grover G. Effects of intracoronary cromakalim on post-ischaemic contractile function and action potential duration. Cardiovasc Res. 1992; 26: 1046–53.
110. Kitakaze M, Weisfeldt ML, Marban E. Acidosis during early reperfusion prevents myocardial stunning in perfused hearts. J Clin Invest. 1988; 82:920–7.
111. Frelin C, Vigne P, Lazdunski M. The role of the Na^+/H^+ exchange system in the regulation of the internal pH in cultured cardiac cells. Eur J Biochem. 1985; 149:1–4.
112. van Emous JG, Schreur JHM, Ruigrok TJC, Van Echteld CJ. Both Na^+-K^+-ATPase and Na^+/H^+ exchanger are immediately active upon post-ischemic reperfusion in isolated rat hearts. J Mol Cell Cardiol. 1998; 30:337–48.
113. Stomer H, de Groot MCH, Horn M, et al. Na^+/H^+ exchange inhibition with HOE642 improves postischemic recovery due to attenuation of Ca^{2+} overload and prolonged acidosis on reperfusion. Circulation. 2000; 101:2749–55.
114. Hartmann M, Decking UKM. Blocking Na^+/H^+ exchange by cariporide reduces Na^+-overload in ischemia and is cardioprotective. J Mol Cell Cardiol. 1999; 31:1985–995.
115. Ferguson JJ. Meeting highlights of the 48th Scientific Sessions of the American College of Cardiology. Circulation. 1999; 100:570–5.
116. Erhardt LR. GUARD During Ischemia Against Necrosis (GUARDIAN) trial in acute coronary syndromes. Am J Cardiol. 1999; 83:23G–25G.
117. Rupprecht HJ, vom Dahl J, Terres W, et al. Cardioprotective effects of the Na(+)/H(+) exchange inhibitor cariporide in patients with acute anterior myocardial infarction undergoing direct PTCA. Circulation. 2000; 101:2902–8.
118. Ehring T, Boehm M, Heusch G. The calcium antagonist nisoldipine improves the functional recovery of reperfused myocardium only when given before ischemia. J Cardiovasc Pharmacol. 1992; 20:63–74.
119. Heusch G. Myocardial stunning: a role for calcium antagonists during ischaemia? Cardiovasc Res. 1992; 26:14–19.
120. Przyklenk K, Kloner RA. Effect of verapamil on post-ischemic "stunned" myocardium: importance of the timing of treatment. J Am Coll Cardiol. 1988; 11:614–23.
121. Park S-W, Tang X-L, Qiu Y, Sun J-Z, Bolli R. Nisoldipine attenuates myocardial stunning induced by multiple coronary occlusions in conscious pigs and this effect is independent of changes in hemodynamics or coronary blood flow. J Mol Cell Cardiol. 1996; 28:655–66.
122. Mak IT, Boehme P, Weglicki WP. Antioxidant effects of calcium channel blockers against free radical injury in endothelial cells. Correlation of protection with preservation of glutathione levels. Circ Res. 1992; 70:1099–103.
123. Gao WD, Atar D, Liu Y, et al. Role of troponin I proteolysis in the pathogenesis of stunned myocardium. Circ Res. 1997; 80:393–9.
124. Matsumura Y, Kusuoka H, Inoue M, Hori M, Kamada T. Protective effect of the protease inhibitor leupeptin against myocardial stunning. J Cardiovasc Pharmacol. 1993; 22:135–42.
125. Gao WE, Liu Y, Marban E: Mechanism of decreased myofilaments Ca^{2+} responsiveness in stunned rat ventricular myocardium: relative roles of soluble cytosolic factors versus structural alterations. Circ Res. 1996; 78:455–65.
126. Neumar RW. Molecular mechanisms of ischemic neuronal injury. Ann Emerg Med. 2000; 36:483–506.
127. Eleff SM, Schleien CL, Koehler RC, et al. Brain bioenergetics during cardiopulmonary resuscitation in dogs. Anesthesiology. 1992; 76: 77–84.
128. Globus MYT, Ginsberg MD, Busto R. Excitotoxic index—a biochemical marker of selective vulnerability. Neurosci Lett. 1991; 127: 39–42.
129. Katz L, Callaway CW, Kagan VE, Kochanek PM. Electron spin resonance measure of brain antioxidant activity during ischemia/reperfusion. Neuroreport. 1998; 9:1587–93.
130. White BC, Winegar CP, Henderson O, et al. Prolonged hypoperfusion in the cerebral cortex following cardiac arrest and resuscitation in dogs. Ann Emerg Med. 1983; 12:414–7.
131. Wolfson SK, Safar P, Reich H, et al. Dynamic heterogeneity of cerebral hypoperfusion after prolonged cardiac arrest in dogs measured by the stable xenon/CT technique: a preliminary study. Resuscitation. 1992; 23:1–20.
132. Salmien A, Liu PK, Hsu CY. Alteration of transcription factor binding activities in the ischemic rat brain. Biochem Biophys Res Commun. 1995; 212:939–44.
133. Kiessling M, Stumm G, Xie Y, et al. Differential transcription and translation of immediate early genes in the gerbil hippocampus after transient global ischemia. J Cereb Blood Flow Metab. 1993; 13:914–24.
134. Krajewski S, Mai JK, Krajewska M, Sikorska M, Mossakowski MJ, Reed JC. Upregulation of bax protein levels in neurons following cerebral ischemia. J Neurosci. 1995; 15: 6364–76.
135. Chen J, Zhu RL, Nakayama M, et al. Expression of the apoptosis-effector gene, Bax, is up-regulated in vulnerable hippocampal CA1 neurons following global ischemia. J Neurochem. 1996; 67:64–71.
136. Chen J, Nagayama T, Jin K, et al. Induction of caspase-3-like protease may mediate delayed neuronal death in the hippocampus after transient cerebral ischemia. J Neurosci. 1998; 18:4914–28.
137. Chen J, Graham SH, Nakayama M, et al. Apoptosis repressor genes Bcl-2 and Bcl-x-long are expressed in the rat brain following global ischemia. J Cereb Blood Flow Metab. 1997; 17:2–10.
138. Krajewski S, Krajewska M, Ellerby LM, et al. Release of caspase-9 from mitochondria during neuronal apoptosis and cerebral ischemia. Proc Natl Acad Sci U S A. 1999; 96:5752–7.
139. MacManus JP, Buchan AM, Hill IE, Rasquinha I, Preston E. Global ischemia can cause DNA fragmentation indicative of apoptosis in rat brain. Neurosci Lett. 1993; 164:89–92.
140. Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med. 1986; 314:397–403.
141. Brain Resuscitation Clinical Trial II Study Group. A randomized clinical study of a calcium-entry blocker (lidoflazine) in the treatment of comatose survivors of cardiac arrest. N Engl J Med. 1991; 324:1225–31.
142. Nellgard B, Wieloch T. Postischemic blockade of AMPA but not NMDA receptors mitigates neuronal damage in the rat brain following transient severe cerebral ischemia. J Cereb Blood Flow Metab. 1992; 12:2–11.
143. Sterz F, Leonov, Y, Safar P, et al. Effect of excitatory amino acid receptor blocker MK-801 on overall, neurologic and morphologic outcome after prolonged cardiac arrest in dogs. Anesthesia. 1989; 71:907–18.
144. Silbergleit R, Haywood Y, Fiskum G, Rosenthal RE. Lack of a neuroprotective effect from N-acetylcysteine after cardiac arrest and resuscitation in a canine model. Resuscitation. 1999; 40:181–6.
145. Lipinski CA, Hicks SD, Callaway CW. Effect of normoxic

ventilation on outcome after asphyxial cardiac arrest in rats. Resuscitation. 1999; 42:221–9.
146. Himi T, Ishizaki Y, Murota S. A caspase inhibitor blocks ischaemia-induced delayed neuronal death in the gerbil. Eur J Neurosci. 1998; 10:777–81.
147. Li H, Colbourne F, Sun P, Zhao Z, Buchan AM, Iadecola C. Caspase inhibitors reduce neuronal injury after focal but not global cerebral ischemia in rats. Stroke. 2000; 31:176–82.
148. Colbourne F, Li H, Buchan AM. Indefatigable CA1 sector neuroprotection with mild hypothermia induced 6 hours after severe forebrain ischemia in rats. J Cereb Blood Flow Metab. 1999; 19:742–9.
149. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med. 1993; 21:1348–58.
150. Xiao F, Safar P, Radovsky A. Mild protective and resuscitative hypothermia for asphyxial cardiac arrest in rats. Am J Emerg Med. 1998; 16:17–25.
151. Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke. 1989; 20:904–10.
152. Kil HY, Zhang J, Piantadosi CA. Brain temperature alters hydroxyl radical production during cerebral ischemia/reperfusion in rats. J Cereb Blood Flow Metab. 1996; 16:100–6.
153. Hicks SD, Parmele KT, DeFranco DB, Klann E, Callaway CW. Hypothermia differentially increases ERK and JNK/SAPK activation in hippocampus after asphyxial cardiac arrest. Neuroscience. 2000; 98:677–85.
154. Leonov Y, Sterz F, Safar P, Johnson DW, Tisherman SA, Oku K. Hypertension with hemodilution prevents multifocal cerebral hypoperfusion after cardiac arrest in dogs. Stroke. 1992; 23:45–53.
155. Zeiner A, Holzer M, Sterz F, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. Stroke. 2000; 3:86–94.