Special Report

Pulseless Electric Activity

Definition, Causes, Mechanisms, Management, and Research Priorities for the Next Decade: Report From a National Heart, Lung, and Blood Institute Workshop

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Sudden cardiac arrest (SCA) remains an important public health challenge. Despite a dramatic decrease in the age-adjusted risk of SCA, the cumulative number of fatal SCAs in the United States remains large. Estimates range from <170,000 to >450,000 fatal SCAs per year; a figure in the range of 300,000 to 370,000 per year is likely the best current estimate.1 SCA appears to account for >50% of all cardiovascular deaths,2 and it is estimated that 50% of the SCAs are the first clinical expression of previously undiagnosed heart disease.2,3 Most out-of-hospital cardiac arrests (80%) occur in private homes or other living facilities.4

Electric mechanisms associated with SCA are broadly classified into tachyarrhythmic and nontachyarrhythmic categories, the latter including pulseless electric activity (PEA; formerly referred to as electromechanical dissociation), asystole, extreme bradycardia, and other mechanisms often associated with noncardiac factors (Table). The first approaches to the problem of SCA focused on ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT). An early impact on the prevention and treatment of VF and VT was realized in patients with acute coronary syndromes >50 years ago,5 followed by the development of strategies for responding to out-of-hospital cardiac arrest, implantable cardioverter-defibrillators, and defibrillation by lay responders.

Data from the Seattle emergency rescue system6 and elsewhere5,8 have identified progressive reductions in the number of responses to SCA over 2 to 3 decades. This change was due primarily to a reduction in the number of ventricular tachyarrhythmic events identified by emergency medical services responders. In the Seattle data, the incidences of PEA and asystole had not changed over the 3 decades of observation and therefore have emerged as proportionately more frequent mechanisms than VT/VF. Whether this also reflects the emergence of greater absolute numbers of PEA and asystole, as suggested in other studies,9–9 possibly as a result of broader deployment of emergency rescue systems with longer average response times, or evolving changes in patient substrate remains to be determined.

As preventive and therapeutic interventions for VT/VF were developing, PEA and asystole did not receive a great deal of attention. Currently, however, PEA should receive greater attention on the basis of the combination of its increasing proportion of the SCA spectrum, its much lower survival rate than that after VT/VF arrests, emerging suggestions that survival may be improved, and uncertainty whether there is a proportional versus an absolute increase in incidence. The definitions, prognostics, and potential for improvements in therapeutic opportunities for PEA, in contrast to asystole, are of sufficient interest and complexity that this condition now warrants a strong investigative focus within the spectrum of SCA mechanisms and management challenges. Expanding mechanism-related concepts offers the hope for both better stratification and development of more effective therapeutic interventions.

Because of the increasing prevalence of and limited scientific information on PEA, the National Heart, Lung, and Blood Institute sponsored a workshop on PEA that convened on June 6, 2012, in Bethesda, MD.10 It was designed to explore current knowledge and future directions for research in the prediction, prevention, and management of PEA, as well as probable mechanistic pathways that might translate to clinical care. The working group participants had expertise in basic, clinical, and epidemiological aspects of SCA generally and PEA in particular. This article summarizes the deliberations, focusing

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.004490/-/DC1.

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(Circulation. 2013;128:2532-2541.)

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.113.004490
On the identification of current scientific gaps and areas that require National Heart, Lung, and Blood Institute leadership, facilitation, and support for scientific and clinical progress.

**Definition of PEA**

At present, there is no single unifying definition for PEA. The common denominator is the presence of spontaneous organized cardiac electric activity in the absence of blood flow sufficient to maintain consciousness and absence of a rapid spontaneous return of adequate organ perfusion and consciousness (see the Table). The latter qualifier excludes transient losses of blood flow such as vasovagal syncope that have clinical implications different from those of true PEA. Therefore, the workshop participants defined PEA as a syndrome characterized by the absence of a palpable pulse in an unconscious patient with organized electric activity other than ventricular tachyarrhythmia on ECG. The definition excludes subjects with nonpulsatile assist devices. ECG patterns associated with PEA vary (Table), and the electric activity may occur at a rate and rhythm that would otherwise be expected to be associated with circulation. The definition of PEA does not include the agonal pattern of slow, very wide QRS complexes at the end of a prolonged cardiac arrest.

**Emerging Epidemiological Patterns of PEA**

Thirty years ago, nearly 70% of the initial ECGs recorded during cardiac arrests showed VF or pulseless VT. Recent data from several large population cohorts including >40,000 patients demonstrate proportions of initial VT/VF in the range of 20% to 25%. In the Seattle study, 61% of cardiac arrests responded to by emergency medical services had VF identified as the initial rhythm in 1979 to 1980 compared with 41% in 1999 to 2000. In contrast, PEA was identified as the initial rhythm in 1979 to 1980 compared with 41% in 1999 to 2000. In parallel with this reduced frequency of VT/VF, recent unpublished data from the Resuscitation Outcomes Consortium and data from the Cardiac Arrest Registry to Enhance Survival network demonstrate an incidence of PEA arrests ranging from 19% to 23%, with the remaining ≈50% of patients initially having asystole.

This striking decline in the frequency of VT/VF and the relative and possibly absolute increase in PEA and asystole as the initial rhythm may be attributable to a number of interacting environmental, clinical, pharmacological, or strategic interventional factors. At least one of these may be analyzed in the context of the location of cardiac arrests. From Resuscitation Outcomes Consortium data based on 12930 total arrests stratified by location, VT/VF occurred in 22% of 9564 arrests occurring in homes, 13% of 1324 occurring in nursing homes, and 14% of 2533 occurring in public locations. Thus, one might conclude that for arrests occurring in public locations and likely benefiting from rapid recognition and management, the incidence of VT/VF is not much lower than 30 years ago. However, patients who have cardiac arrests in the home or in a nursing home, where the incidence of VT/VF is reduced, may be older, may have more severe chronic conditions, or may be subject to delays in recognition and initial responses. The decline in VT/VF may also be contributed to by the increase in implantable cardioverter-defibrillators in patients with systolic heart failure and the increasing use of aggressive pharmacological management of heart failure, particularly β-blockers, which may suppress VT/VF and result in an increase in cardiac arrests related to both PEA and asystole. However, these potential determinants of the increasing burden of PEA need further investigation.

The overall Resuscitation Outcomes Consortium survival rate for treated patients with PEA arrests surviving to hospital discharge was ≈8%. This compares with 30.5% for VT/VF arrests. Survival from PEA arrests in public settings was 14.9% and from arrests in the home was 7.5%. Similar low survival rates were reported by the Cardiac Arrest Registry
to Enhance Survival Network.\textsuperscript{15} However, data from 1 report suggest that survival from PEA arrests appears to be improving over time. Among 627 PEA arrests treated in Seattle from 2000 to 2004, survival to 1 month was 9.9% and survival to 1 year was 6.2%. In the period from 2005 to 2010, of 760 PEA arrests, 14.6% of patients survived to 1 month and 11.5% survived to 1 year.\textsuperscript{17} The adjusted odds ratio (OR) for improved survival across the 2 periods was 1.51 (95% confidence interval [CI], 1.07–2.11) at 1 month and 1.90 (95% CI, 1.27–2.85) at 1 year. There were similar improvements in the frequency of return of spontaneous circulation (ROSC), survival to discharge, and cerebral performance category 1 to 2 at discharge. The authors of this study attribute the increase in survival rates to the improvement in resuscitation techniques over the past decade. In a study of in-hospital cardiac arrests in pediatric and adolescent subjects <18 years of age between 2000 and 2009, an increase in the frequency of PEA was observed that was associated with an increase in survival to hospital discharge over time.\textsuperscript{18}

Mechanisms and Pathophysiology of PEA
Defining the pathobiology and management of PEA has been limited by the lack of clinically relevant laboratory models. Asphyxia is the traditional experimental method of inducing PEA arrest, and this model, in various forms, has been used since the 1960s.\textsuperscript{19} However, asphyxia is not a common clinical cause of out-of-hospital PEA arrest in the adult population. In autopsy studies, ≈50% of cases of PEA may be ascribed to a primary cardiac event.\textsuperscript{20} In 1 study, PEA as the initial rhythm was observed in 50% to 60% of cardiac arrests with onsets witnessed by advanced rescuers (paramedics) and was not preceded by a reported respiratory event.\textsuperscript{21} Finally, up to one third of patients resuscitated from cardiac arrest caused by PEA undergo a percutaneous intervention for acute coronary occlusion and ST-segment–elevation myocardial infarction, suggesting that PEA may be an initial arrhythmic event resulting from acute ischemia.\textsuperscript{22} In the 1980s, PEA after countershock of prolonged, untreated VF was introduced as a method for studying its pathophysiology.\textsuperscript{23,24} This model does not replicate primary PEA; it is more similar to PEA after a shock terminating prolonged VF. Observations during resuscitation after postshock PEA have demonstrated evidence of metabolic and electrolyte disturbances that could sustain PEA after defibrillation.\textsuperscript{25} Whether these are causes, conditioning influences, or therapeutic targets requires further clarification. A possible role of the parasympathetic nervous system in primary PEA has been indirectly evaluated in an asphyxia model in which surgical or chemical (high-dose atropine) vagotomy was performed after the induction of PEA with asphyxia. ROSC was more likely after surgical vagotomy, but high-dose atropine had no beneficial effect. The mechanistic benefit of vagotomy was unclear.\textsuperscript{26}

The apparent increase in PEA over the last 2 decades has paralleled the increasing use of β-blockers and other medications for the management of ischemic heart disease and congestive heart failure. The potential relationship between drug therapy and the apparently increasing incidence of PEA is important. Only 1 laboratory study has attempted to evaluate the impact of long-term drug therapy (propranolol and captopril) on the outcome of ischemia induced by coronary occlusion in a rat model.\textsuperscript{27} Although prearrest drug therapy increased the VF threshold in the animal model, it is unclear from the reported data whether the study drugs facilitated the occurrence of PEA.\textsuperscript{28} Drugs affecting the central nervous system have been implicated recently, but further studies are needed to define any causal relationships.

**Cellular Mechanisms and Contractile Dysfunction**
For some time, acute coronary occlusion has been known to result in a sudden loss of contractile force. The most likely cause is abrupt loss of tissue turgor, also known as the reverse garden hose effect.\textsuperscript{29} The mechanism underlying the garden hose effect is uncertain but may be related to loss of optimum cross-bridge overlap (eg, Starling mechanism) when the erectile effect of the vasculature is abrogated. Because intracellular calcium (Ca\textsuperscript{2+}) is critical for regulating myocardial contraction\textsuperscript{30} (see Appendix I in the online-only Data Supplement), an alternative hypothesis is that loss of vascular pressure alters vasotropic feedback, which modulates triggered Ca\textsuperscript{2+} entry or myofilament Ca\textsuperscript{2+} sensitivity. Metabolic consequences of ischemia likely contribute to further contractile dysfunction\textsuperscript{31} (see Appendix II in the online-only Data Supplement). This may be of particular importance for PEA following countershock after prolonged VF. It is important to recognize that many of the metabolic changes are also associated with chronic heart failure.\textsuperscript{32,33} Thus, metabolic stress could contribute to loss of contractility, leading to PEA in patients with advanced heart failure.

Inotropic agents, particularly β-agonists, have been the mainstay of therapy for PEA\textsuperscript{34} on the basis of considerations of molecular factors involved in contractile function and dysfunction. β-Agonists phosphorylate L-type Ca\textsuperscript{2+} channels, ryanodine receptors, the sarcoplasmic reticulum calcium ATPase regulator phospholamban, and myofilaments not only to increase trigger Ca\textsuperscript{2+} entry into the cell but also to synchronize Ca\textsuperscript{2+} release from a loaded SR and improve myofilament Ca\textsuperscript{2+} responsiveness. There is, however, a time-dependent loss of contractile function in response to the metabolic stress of acute ischemia. Because the mechanisms for this loss are unknown, further studies to elucidate these mechanisms are needed to provide a rational basis for future therapies. In addition, whether myofilament Ca\textsuperscript{2+} sensitizers such as levosimendan or other agents may be of additional or greater benefit in the setting of PEA has yet to be determined.

PEA may occur when the host response to a dramatic stress on the cardiovascular system is inadequate or inappropriate. An important response that was recently recognized is overwhelming stress leading to rapid activation of the intrinsic immune system, causing direct acute depression of cardiac function or decoupling of electromechanical synchrony, resulting in PEA. Innate immune activation also produces cardiokines, which in circulation may lead to profound vaso-dilation and ventricular arterial decoupling, also setting the stage for arrhythmias.\textsuperscript{35} Recent understanding of the signaling pathways involved in innate immune activation offers potential areas of further research and therapy.
Clinical associations between the presence of inflammatory cytokines and SCA have been established. In the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial, elevation of cytokines such as osteoprotegerin was the best predictor of early sudden death after myocardial infarction. Furthermore, the proposed benefit of N-3 fatty acids on cardiac mortality after myocardial infarction and in heart failure has also been attributed at least partially to the anti-inflammatory effects of N-3 fatty acids.

The production of cytokines/cardokines such as tumor necrosis factor and the interleukin family of cytokines may acutely depress cardiac function. This has been attributed to the effect on phosphatidylinositol 3 kinase isoforms and lipid-signaling intermediates such as sphingosine-1, which may directly interfere with Ca\textsuperscript{2+} signaling. More recently, there have been data to suggest that the high-mobility group box 1 or alarmin family of signals may also directly depress cardiac function and Ca\textsuperscript{2+} kinetics. However, this effect may be partially ameliorated through phosphatidylinositol 3 kinase-γ blockade, suggesting possible avenues for host protection.

There has been a significant interest in the role of hormones, namely relaxin, in SCA. This natural hormone increases in women during pregnancy and has been studied in acute heart failure. Its mechanisms of action are not well known. In the setting of acute ischemic arrest, relaxin was able to significantly reduce the adverse outcomes of asystole, ventricular tachyarrhythmias, or bradycardiac arrests, possibly through anti-inflammatory effects by inhibiting mast cell activation.

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

In contrast to VT/VF for which electric arrhythmogenesis may be associated with channelopathies, there are no specific channel dysfunction mechanisms currently known to contribute to the rapid loss of contractile function associated with PEA. However, one could hypothesize and test for the functional changes in L-type Ca\textsuperscript{2+} channels and ryanodine receptors described in Appendix II in the online-only Data Supplement as acquired channel defects. Even more speculative is the possibility that genetic susceptibilities to rapid reductions in L-type Ca\textsuperscript{2+} channel and ryanodine receptor activity, in response to metabolic stress, result in a more profound contractile failure in some individuals compared with others.

**Risk Factors**

Older age is more likely to be associated with PEA and asystole than with VF or VT, and the proportion of PEA among cases of SCA increases with age: from 10% to 12% in those 13 to 49 years of age to 18% in those ≥50 years of age. In addition, an analysis from the Oregon Sudden Unexpected Death Study (Oregon SUDS) showed that older age was a significant predictor of future PEA after adjustment for other demographic variables, arrest circumstances, and comorbidities.

Sex is also associated with the presenting arrhythmia during SCA. Several studies have shown that women are significantly more likely than men to manifest PEA. In the Oregon SUDS, approximately one third of women presented with PEA, and after adjustment for demographics, Utstein data elements, and disease burden, female sex remained a significant predictor of PEA (OR, 1.48; 95% CI, 1.05–2.09). However, women appear to have a survival advantage over men for SCA resuscitation outcomes. Even though women are more likely to manifest with PEA and rates of successful resuscitation are significantly lower after PEA compared with VT/VF, rates of survival from overall cardiac arrest are significantly higher in women compared with men (OR, 1.85; 95% CI, 1.12–3.04).

Several studies report an association between black race and the propensity to present with PEA. In 3 suburban counties in Michigan, 21% of blacks versus 14% of whites presented with PEA. In the Oregon SUDS, black race was strongly associated with PEA as opposed to VF (OR, 2.64; 95% CI, 1.29–5.38) after adjustment for age, sex, resuscitation variables, and comorbidities.

Hypoxia has long been recognized as a component of PEA pathophysiology, which may explain why pulmonary disease is a significant independent predictor of PEA. In the Oregon SUDS, men with pulmonary disease were 3-fold more likely than men without pulmonary disease to have PEA (versus VF/VT) as their presenting arrhythmia (OR, 3.17; 95% CI, 1.86–5.42). In another study that examined the association of SCA with deterioration resulting from chronic obstructive pulmonary disease, 40% presented with PEA. In a small autopsy series, significant pulmonary disease was observed in 20% of patients with PEA.

In a retrospective analysis from the Oregon SUDS, a lifetime clinical history of syncope was identified as a novel association with PEA and remained a significant determinant of PEA after adjustment for other conditions (OR, 2.64; 95% CI, 1.31–5.32). The preponderance of syncope among PEA cases was not explained by an increased prevalence of conduction system disease, leading to the interesting possibility that in a subgroup of patients, severe hypotension caused by peripheral vascular failure or a malignant form of vasovagal syncope may account for manifestation with PEA.

There is conflicting information on the role of medications in the pathophysiology of PEA. A study from Youngquist et al analyzed the prevalence of prescription medications among 179 cases of SCA and reported that 49% of patients with PEA were on β-blockers compared with 20% of VF patients. However, this univariate analysis was based on a complex statistical analysis that did not specifically adjust for drugs other than β-blockers and calcium channel blockers or other conditions. Recently, the Oregon SUDS group reported results from a comprehensive assessment of prescription drugs in a larger population of >800 patients, also accounting for the presence of cardiac/noncardiac disease conditions. Specific classes of medications with either negative or positive cardiac inotropic effects were evaluated for association with occurrence of PEA versus VF/VT. In multivariate analyses, the use of...
antipsychotic drugs was a significant and independent risk factor for PEA, possibly related to their negative inotropic effects. In contrast to other studies, no relationship was identified between β-blocker use and the occurrence of PEA in this study.

Clinical Expression and Subsets

PEA is classified primarily as cardiac and noncardiac in origin and is subclassified according to specific causes in each category. Noncardiac causes of PEA include profound hypovolemia such as major bleeding caused by a ruptured aortic aneurysm, or by trauma or obstruction to the circulation resulting from massive pulmonary embolism, cardiac tamponade, or tension pneumothorax. The initial rhythm accompanying PEA resulting from these causes is generally sinus tachycardia, which evolves to severe sinus bradycardia, PEA, asystole, and ultimately death in the absence of an intervention. The clinical history guides the differential diagnosis. In these settings, myocardial contractile function may be normal or mildly to moderately impaired, but the heart is generally able to generate a reduced pulse pressure and to return to normal or near-normal function with volume repletion or obstruction relief. Early identification of treatable conditions is critical for survival. The workshop did not address these states.

PEA resulting from cardiac causes is classified as primary when it is the initial mechanism of a cardiac arrest or secondary when it follows spontaneous or electric termination of VT/VF. It is difficult to distinguish whether PEA after shock therapy is secondary to myocardial injury/mechanical paralysis caused by the shock or reperfusion or merely the manifestation of end stage pump failure after VT/VF has been terminated by a defibrillation shock. Insights into this distinction and the determination of the potential clinical relevance require further study. In patients with implantable defibrillators who died suddenly, 16% of the deaths were attributable to primary PEA, and 30% of those patients had postshock PEA. Postshock PEA was associated with a lower left ventricular ejection fraction and a greater prevalence of symptomatic heart failure. The determinants and mechanisms of primary cardiac PEA in patients without severe heart failure require further study and are areas of inquiry with the potential to develop interventions to improve survival.

Clinical and Experimental Management Strategies

The guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care provide management algorithms that have similar initial stages but diverge once shockable or nonshockable rhythms are identified. The presence of a shockable rhythm calls for rapid deployment of a defibrillator with some variation in preshock actions determined by the circumstances of individual cases. An initial nonshockable rhythm calls for continued CPR with a concomitant rapid evaluation to identify and manage reversible noncardiac causes such as hypovolemia, trauma, vascular obstruction, and acute respiratory failure. These mechanisms are commonly characterized by the presence of PEA with residual left ventricular contractions and may respond well to reversal of the inciting causes combined with drugs that improve contractility. In the absence of a specific therapy for the reversal of PEA, analogous to failed electric intervention for VT/VF, various support therapies for maintaining viability and central nervous system function are being developed and evaluated in parallel with new approaches to PEA. The support therapies are not specific for PEA, having implications for asystole and resistant VT/VF also, but they are particularly important for PEA.

Resuscitation guidelines emphasize the need to identify and treat other potentially reversible causes of PEA while performing standard resuscitation. These include acute myocardial ischemia, acidosis, hypoxia, hyperkalemia and hypokalemia, hypothermia, hypoglycemia, hypocalcemia, and toxins/drug overdose. Significant hyperkalemia, hypocalcemia, and hypoglycemia, however, are not commonly associated with PEA.

The presence of residual left ventricular contraction during resuscitation from SCA may be identified by emergency echocardiographic techniques. The absence of residual left ventricular contraction is common in secondary (postdefibrillation) PEA. This circumstance has a lower probability of responding to currently available therapies for PEA and has an ominous prognosis. Less is known about the causes and therapeutic opportunities in primary PEA, in which it is the mechanism present at the onset of cardiac arrest. It is generally assumed that primary PEA in the setting of end-stage heart disease and postdefibrillation PEA characterized by restoration of sinus or junctional electric mechanisms without a pulse are a consequence of the extent of underlying disease and are not generally amenable to successful interventions with currently available therapies.

Because PEA is a common mechanism of SCA associated with massive pulmonary embolism, consideration has been given to the use of thrombolytic therapy when responding to PEA. This concept is particularly rational when there is suspicion of pulmonary embolism as the mechanism, although studies to date have not shown any benefit for the use of thrombolysis during cardiac arrest when all presenting rhythms were included or when just PEA was included. However, the latter study was small; on the basis of its limited clinical and autopsy data, the incidence of pulmonary embolism appeared to be very small. Further studies are needed to determine efficacy. Risk-versus-benefit estimates of its use for high-probability pulmonary embolism cases are also necessary because hypovolemia secondary to blood loss is another cause of noncardiac PEA that may be difficult to distinguish during initial responses.

Finally, even less is known about primary PEA as the mechanism of onset of cardiac arrest in acute coronary syndromes. Whether this is a consequence of a decreased incidence of VT/VF in this setting, possibly related to β-blocker therapy, in conjunction with systemic circulating cardiodepressive signals remains to be elucidated. This area of the PEA spectrum invites investigative efforts into mechanisms and future specific therapies.

CPR: Chest Compressions

Numerous studies have shown that improved blood flow during CPR results in increased survival. Standard chest
compression techniques, including newly introduced modifications such as hands-only CPR, are the mainstay of conventional strategies. Mechanical devices offer more consistent chest compressions, potentially increasing blood flow during CPR with the potential to improve survival, although further study is required. This is especially relevant for PEA because a rapid ROSC is more difficult to achieve with nonshockable SCA mechanisms. The ability to achieve and reliably monitor sufficient and consistent blood flow is central to improving outcomes from SCA regardless of mechanism or cause.

Monitoring Cardiac Motion During CPR
The ability of echocardiography and capnography to predict survival of cardiac arrest patients in the emergency department has been studied (see Appendix III in the online-only Data Supplement). Of the 2 diagnostic tests, only capnography was a significant predictor of survival. Both the echocardiographic detection of cardiac activity and end-tidal carbon dioxide levels >16 mm Hg were significantly associated with improved resuscitation in the emergency department, but stepwise logistic regression analysis demonstrated that prediction of survival with capnography was not enhanced by the addition of echocardiography. However, both strategies should be studied further in light of the observation of enhanced in-hospital survival with longer resuscitation efforts.60 Echocardiography and capnography may help to identify subgroups with better or worse survivability and potentially to define futility of continued resuscitation.

CPR: Mechanical Devices
There has been interest in recent years in the development and application of mechanical devices for use in CPR responses. The general concept is to achieve uniformity and maximum efficiency in circulatory support during prolonged arrests. The strategy appears most appropriate for victims in whom prompt electric restoration of rhythm is not feasible, particularly PEA and asystole.

Active Compression and Decompression CPR
Active compression and decompression CPR uses the addition of an integral suction cup that provides active return of the chest to the neutral, uncompressed position. The theory behind this intervention is that the active decompression generates negative intrathoracic pressure during chest decompression that augments venous return and increases forward flow on the next compression. Laboratory studies have shown improved hemodynamics with the use of the device.53 There are manual versions of this device, as well as electrically and pneumatically operated versions.64 One trial has shown improved survival to discharge when active decompression from a manual device was combined with the impedance threshold device, the latter enhancing the negative intrathoracic pressure generated during chest decompression.55

Load-Distributing Band
A load-distributing band device is designed to allow substantial additional force to be applied to the chest by distributing the force over most of the chest. Recent trials showed improved hemodynamics, with coronary perfusion pressures above the level generally associated with improved survival. Clinical trial results have been mixed and are dependent on the way that the studies are implemented.

Because of the greater dependence on CPR in PEA, these technologies may be more important for subgroups of patients with SCA caused by nonshockable rhythms. In addition, these automatic mechanical devices are intended to provide high-quality CPR during ambulance transport. Enhancements to the devices that are needed to make substantial differences in outcomes include reducing costs, improving blood flow—generating capabilities, reducing interruptions in chest compression, and reducing deployment time.

Synchronized Chest Compression
In addition to the use of mechanical devices, the use of chest compressions synchronized to residual cardiac contractions has been investigated as a way of further augmenting blood flow during CPR. A porcine model of controlled progressive hypoxia was used to induce PEA with peak aortic pressures targeted to 50 mm Hg, which is below the level that produces a palpable pulse.57 Systolic synchronization was associated with statistically significant increases in relaxation-phase aortic pressure and coronary perfusion pressure. Thus, synchronizing chest compressions with residual cardiac activity may augment blood flow and survival, and further studies are needed to define the role of synchronized chest compression in treating PEA. Whether synchronized enhancement of contractions at a slower PEA rate is equivalent to or better than standard unsynchronized CPR compressions at a rate of ≈100 compressions per minute remains to be determined.

Standard Pharmacological Interventions
Vasoconstrictors have been studied extensively for improving blood flow and outcomes from CPR, including PEA, but little is known about the hemodynamics during clinical resuscitation. For example, resuscitation guidelines call for repeated doses of epinephrine during CPR in the absence of an obvious “treatable cause” of PEA, even though rescuers usually have no way of knowing either the patient’s inotropic status or whether the patient’s systemic vascular resistance is high or low. Vasoconstrictors augment blood flow and survival in animal models but have not been associated with improved survival in clinical trials, potentially because of their late administration, after the patients were no longer viable, and potentially also because of inconsistent chest compressions and concomitant variable amounts of blood flow generated by chest compression.

Experimentally, epinephrine was compared with vasopressin after 15 minutes of cardiac arrest and 3 minutes of chest compression in 18 pigs randomly treated with 0.8 U/kg vasopressin or 200 μg/kg epinephrine. Spontaneous circulation was restored in 8 of 9 in the vasopressin group and 1 of 9 in the epinephrine group (P = 0.003). Vasopressin significantly increased left ventricular myocardial and total cerebral blood flow during CPR and ROSC. In 2 clinical studies, epinephrine increased the rate of ROSC, but it did not increase
survival to hospital discharge. In another study, an increase in the dose of epinephrine during resuscitation of patients with asystole and PEA was an independent risk factor for unfavorable functional outcome and mortality. In a study comparing vasopressin and epinephrine for SCA without return of circulation, the 2 drugs performed similarly for victims with VF and PEA, but vasopressin performed somewhat better for asystole. There was also a suggestion that vasopressin followed by epinephrine may have added benefit in victims of refractory cardiac arrest. A subsequent study comparing the combination of epinephrine and vasopressin with epinephrine alone did not demonstrate added benefit for the combination, but asystole was identified as the initial rhythm in 83% of the patients, so the potential benefit for VF and PEA remains unknown. Further studies of the role of vasopressors in PEA might clarify their potential benefit.

Sodium nitroprusside is a vasodilator that may reduce ischemia and may have direct tissue salvage effects. The added benefit of sodium nitroprusside with enhanced CPR on 24-hour survival rates after cardiac arrest was studied in an experimental pig model. Enhanced CPR was defined as the inclusion of active compression-decompression CPR, an inspiratory impedance threshold device, and abdominal binding. Sodium nitroprusside with enhanced CPR significantly improved hemodynamics, resuscitation rates, and 24-hour survival rates with good neurological function after cardiac arrest compared with standard CPR or enhanced CPR alone. Whether sodium nitroprusside with enhanced CPR will improve survival outcomes in clinical cardiac arrests resulting from PEA requires further study.

Atropine is generally no longer recommended for PEA. In 1029 adults with PEA from the Survey of Survivors After Out-of-Hospital Cardiac Arrest in the Kanto Area, Japan (SOS-KANTO) study, the use of atropine with epinephrine was associated with a significantly lower 30-day survival rate than the use of epinephrine alone.

**Newly Emerging Pharmacological Interventions**

Cyclosporine is a promising drug on the basis of the concept that PEA in many instances results from myocardial damage during reperfusion, somewhat similar to the basis for postconditioning (see below). Cyclosporine inhibits the formation of mitochondrial permeability transition pore, a key component of lethal reperfusion injury, in response to the calcium overload and reactive oxygen species that allow damage to mitochondria. Its relevance may be related to an observation of reduced infarct size in patients with ST-segment-elevation myocardial infarction after reperfusion. Reperfusion injury may have a pathophysiology similar to that which occurs in some patients who develop PEA after defibrillation.

Curcumin, a polyphenolic compound derived from turmeric, may have protective effects against myocardial injury through attenuation of oxidative stress and inflammation. It is a selective inhibitor of Toll-like receptor 2, a receptor membrane protein expressed on the cell surface that recognizes foreign substances and then signals a response from cells of the immune system. In 1 study, Sprague-Dawley rats were fed curcumin 1 week before cardiac ischemia/reperfusion injury. Cardiac contractility, connexin43, fibrosis, and other variables improved compared with a control group. These results suggest that selective inhibition of Toll-like receptor 2 by curcumin could be preventive and therapeutic for myocardial injury and thereby for PEA.

**Critical Tissue Protection**

**Intra-Arrest Hypothermia**

Hypothermia induced after ROSC has been shown to improve outcomes. There are generally many hours of delay in achieving therapeutic hypothermia after successful resuscitation, and earlier induction of hypothermia may enhance its therapeutic benefits. The effects of intra-CPR hypothermia with and without volume loading on ROSC and infarction size were investigated in a coronary occlusion model of cardiac arrest (see Appendix IV for details). The results suggest that intra-CPR hypothermia significantly reduces myocardial infarction size. Elimination of volume loading further improves outcomes. Given the substantial benefit that may be achieved with intra-CPR induction of hypothermia, improved methods for generating intra-CPR hypothermia are needed. The techniques should be sufficiently simple to use that they may be used out of the hospital by responders.

**Extracorporeal Oxygenation**

For patients who have received adequate conventional or mechanically supported CPR initiated early after the onset of PEA without ROSC up to hospital arrival, the potential benefit of extracorporeal membrane oxygenation should be evaluated. This is viewed as adjunctive to other strategies such as induced hypothermia.

**Postarrest Conditioning**

Ischemic postconditioning with “stuttering” reintroduction of blood flow after prolonged ischemia has been shown to offer protection against ischemia/reperfusion injury to the myocardium and brain. Four 20-second pauses during the first 3 minutes of standard CPR was studied as a method for improving postresuscitation cardiac and neurological function in a porcine model of prolonged untreated cardiac arrest. Eighteen pigs that were intubated and anesthetized with isoflurane had 15 minutes of untreated VF followed by standard CPR (see Appendix V in the online-only Data Supplement). Animals receiving standard CPR plus postconditioning had statistically significant improvement in left ventricular ejection fraction at 1 and 4 hours compared with animals receiving standard CPR alone. Neurological function at 24 hours also significantly improved with standard CPR plus postconditioning compared with standard CPR alone. Similar data were obtained in a postcountershock model of PEA. Thus, ischemic postconditioning improved postresuscitation cardiac function and facilitated neurological recovery after 15 minutes of untreated cardiac arrest in pigs. This type of controlled pauses in chest compression is an intriguing and potentially promising method for improving outcomes and should be studied further.
Summary and Future Research Opportunities

On the basis of the current state of knowledge of PEA, in conjunction with its increased prevalence compared with tachyarhythmic cardiac arrest, its historically poor outcome, and emerging suggestions that opportunities for better outcomes may be feasible, the working group made a series of recommendations that constitute a road map for future research.

The workshop participants produced a working definition of the PEA syndrome and, on the basis of the literature, support the differentiation of primary and secondary forms of PEA. It was recognized that many different experimental and clinical conditions may lead to the PEA syndrome. However, it is not clear whether there is a final common pathway at the cellular level for each of these conditions. Traditional experimental models of the PEA syndrome differ substantially from conditions in the majority of clinical cases. The Oregon SUDS, the Cardiac Arrest Registry to Enhance Survival, the Resuscitation Outcomes Consortium, and surveillance data on medication use before arrest suggest that there may be important patient “host factors” associated with PEA as the initial documented cardiac arrest rhythm. These observations are intriguing, but it is not clear whether these associations signal a causal relationship that may provide insight into the pathophysiological mechanisms underlying PEA. Several relatively simple and inexpensive modalities, potentially useful for further PEA classification, are readily available. Echocardiographic and end-tidal carbon dioxide observations provide real-time insight into the potential causes and prognosis of PEA, but little is known about the hemodynamics during clinical resuscitation. Therefore, methods to estimate the inotropic status and systemic vascular resistance during resuscitation would be potentially useful.

The working group makes the following recommendations:

1. Develop a taxonomic classification of the known experimental and clinical conditions associated with PEA.
2. Conduct future experimental and clinical studies and report them using this taxonomic classification.
3. Identify new experimental models that better mimic the clinical conditions leading to the syndrome of PEA to elucidate the intracellular pathways that result in the syndrome of PEA. Development and refinement of such models should be a high priority, contributing to the design of pilot studies in humans.
4. Capture and analyze accurate additional data elements in existing and future cardiac arrest surveillance, notably prior illnesses and current medications, to further elucidate the relationship between patient host factors and the initial documented cardiac arrest rhythm.
5. Collect genetic, proteomic, and biomarker data on both experimental models and clinical subjects that may lead to a better understanding of the pathophysiology of PEA.
6. Obtain real-time hemodynamic information during resuscitation, particularly when PEA occurs, to guide pharmacological management. Perform noninvasive technologies such as bioimpedance and bioreactance in experimental cardiac arrest and PEA models to determine whether they can track hemodynamics accurately enough during low-flow states to be of potential use clinically. For those with promising results, consider conducting clinical studies of hemodynamically guided pharmacological intervention (e.g., vasoconstrictor/vasodilator/inotropic therapy) during PEA.
7. Consider the merits of pilot testing of PEA-specific interventions in humans on the basis of promising experimental data such as synchronized mechanical chest compression and vasodilator therapy.
8. Conduct experimental and pilot clinical studies focusing on earlier application of therapeutic hypothermia, particularly when initiated during ongoing resuscitation.

As a general principle, adequate pilot data are needed to justify the investment in large clinical trials addressing the multiple aspects of PEA cited in this article. This warrants the support of smaller, hypothesis-generating studies addressing prevention and treatment of PEA. The goal of support for hypothesis-generation studies, in parallel with hypothesis-testing studies, is to identify pathways worthy of investigation into this problem of major public health significance.

Disclosures

Dr Halperin receives consultant fees and grant support from Zoll Circulation, Inc. Dr Gillis receives research support from Medtronic, Inc. Dr Walcott receives research support from Physio-Control, Inc. The remaining authors report no conflicts.

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KEY WORDS: arrhythmias, cardiac arrest, death, sudden, cardiac arrest
Supplemental Material

Supplemental Appendix 1:
The extent of SR calcium release and force development with each beat is regulated in large part by the extent of calcium entry.\(^1\) A larger Ca\(^{++}\) current recruits more couplons, sites located throughout the ventricular myocytes where Ca\(^{++}\) channels on the sarcolemma are closely apposed to ryanodine receptors on the internal SR membrane. This results in greater Ca\(^{++}\) release and thereby produces a larger calcium transient.\(^2\)

References

Supplemental Appendix 2:
Ischemia is associated with a rapid decline in high energy phosphates such as phosphocreatine and ATP, followed by rapid accumulation of ADP and metabolites such as Mg\(^{2+}\), H\(^+\), P\(_i\) and lactate.\(^1\) Increases in H\(^+\) and P\(_i\) reduce myofilament calcium responsiveness so that normal delivery of calcium is less effective at inducing contraction and force development.\(^2,3\) The increase in ADP and the reduction in ATP also slow relaxation. Continued metabolic stress causes a reduction in LCC open probability and an increase in LCC latency leading to delayed and reduced calcium entry into the diadic cleft.\(^4\) Meanwhile Mg and H\(^+\) accumulation reduces the sensitivity of RyRs to calcium.\(^5\) The reduction in RyR sensitivity combined with the delayed, dysynchronous and reduced entry of trigger calcium leads to dysynchronous release of calcium from independent release sites (couplons) located throughout the cell.\(^6\) Thus the reduction of myofilament responsiveness is compounded by the reduction and uneven delivery of calcium to myofilaments in different locations of the cell, resulting in further loss of developed force. One
additional consideration is that the increased ADP:ATP ratio will compromise SERCA, thereby lowering SR calcium stores over time and compromising subsequent calcium transients.

References


Supplemental Appendix 3:

One hundred two, nonconsecutive cardiac arrest patients prospectively underwent either cardiac ultrasonography alone or in conjunction with capnography during cardiopulmonary resuscitation at two community hospital EDs with emergency medicine residency programs. All patients underwent echocardiographic evaluation, ranging from one to five scans, during the cardiac resuscitation. Fifty-three patients also had capnography measurements recorded. The presence of echocardiographically identified residual contractions at any point during the resuscitation was associated with better survival to hospital admission, 11/41 or 27%, in contrast to those without cardiac activity, 2/61 or 3% (p < 0.001). Higher median ETCO(2) levels, 35 torr, were associated with improved chances of survival than the median ETCO(2) levels for nonsurvivors, 13.7 torr (p < 0.01).
Reference

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Supplemental Appendix 4:

Myocardial staining was used to define the area at risk and myocardial necrosis. Group A had no intervention. Immediately after return of spontaneous circulation, group B received surface cooling with cooling blankets and ice. Group C received intra-CPR 680 mL of 28°C 0.9% normal saline via a central venous catheter. Group D received intra-CPR 673 mL of 4°C normal saline followed by surface cooling after return of spontaneous circulation. Group E received intra-CPR and hypothermia after return of spontaneous circulation with an endovascular therapeutic hypothermia system placed in the right atrium and set at a target of 32°C. Intra-CPR volume loading with room temperature (group C) or iced saline (group D) significantly (*P* < 0.05) decreased coronary perfusion pressure (group C, 12.8 ± 4.78 mm Hg; group D, 14.6 ± 9.9 mm Hg) compared with groups A, B, and E (20.6 ± 8.2, 20.1 ± 7.8, and 21.3 ± 12.4 mm Hg). Return of spontaneous circulation was significantly improved in group E (9 of 9) compared with groups A plus B and C (10 of 18 and 1 of 8). The percent infarction to the area at risk was significantly reduced with intra-CPR hypothermia in groups D (24.3 ± 4.2%) and E (4 ± 3.4%) compared with groups A (72 ± 5.1%) and B (67.3 ± 4.2%).

Reference


Supplemental Appendix 5:

Nine animals were randomized to receive PC with four, controlled, 20-s pauses, during the first 3 min of CPR (SCPR+PC). Resuscitated animals had echocardiographic evaluation of their ejection fraction after 1 and 4 h and a blinded neurological assessment with a cerebral
performance category (CPC) score assigned at 24 and 48h. All animals received 12h of post resuscitation mild therapeutic hypothermia.1

Reference