The PULSE Initiative
Scientific Priorities and Strategic Planning for Resuscitation Research and Life Saving Therapies

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The Post-resuscitative and initial Utility in Life Saving Efforts (PULSE) Conference represented an initiative by leaders of the international scientific community who sought opportunities for major improvements in clinical outcomes after cardiopulmonary resuscitation and after resuscitation from serious traumatic injury.1 The experts focused on scientific research that would yield major advances in lifesaving care, including measurable increases in survival and functional recovery. However, unless research support is prioritized to address resuscitation, it is highly unlikely that these opportunities would soon be realized.

We lose more than 1000 lives each day in the United States from sudden, unexpected death, a fatality rate comparable to the crash of two 747 aircraft without survivors.2–5 Cardiovascular disease is the leading cause of death among individuals aged greater than 65 years, the second leading cause of death among individuals aged 45 to 65 years, and the 5th leading cause of death among individuals aged 1 to 9 years.4,5 Traumatic injuries in the United States were responsible for 147,891 deaths and 2.6 million hospitalizations, costing over $335 billion per year and resulting in 37 million emergency department visits in 1995.6–7 Trauma is the leading cause of death among children and all individuals to age 34 years, the leading cause of loss of productive life-years of any disease, with societal costs (estimated by the National Safety Council) of $469 billion dollars annually, and the third leading cause of death among individuals aged 45 to 65 years, and the 5th leading cause of death among individuals aged 1 to 9 years.4,5

A Consensus Definition of Resuscitation Science
Resuscitation science is the study of the epidemiology, pathophysiology, mechanisms, and improved management of the sudden states of illnesses or injuries, which result in impending or actual cessation of oxygen delivery. These events are characterized by profound compromise in cardiopulmonary and cerebral function. Resuscitation science especially addresses mechanisms, diagnoses, and management of clinical and experimental pathophysiological states of whole body oxygen deprivation. Such clinical events typically occur without prior warning and they affect age groups ranging from neonates to senior adults. Immediate life-threatening illnesses and injuries have many precipitating causes, including cardiac arrest, respiratory failure, hemorrhagic blood loss, neurological injury, and traumatic injuries to soft tissues and the bony skeleton.

Resuscitation research therefore encompasses investigations of mechanisms with a focus on conditions that initiate, mediate, and result from whole body hypoxia and multiorgan ischemia. Precipitating events must therefore be identified. Better methods are needed to actively intervene to interrupt the injurious process, promptly restore cardiopulmonary and cerebral function, and at the same time mitigate reperfusion injury. The intent is to minimize tissue injury and maximize tissue and organ repair. This research also addresses the large

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A complete list of PULSE participants, working groups, and leadership can be found in the online-only Data Supplement available at http://www.circulationaha.org

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human and monetary costs, including morbidity and mortality, both in terms of individual burden and societal costs. Resuscitation research will require basic laboratory investigations, the utilization of animal models, clinical trials, and epidemiological investigations. The goal is to decrease mortality, morbidity, and both human and monetary costs of cardiopulmonary arrest and traumatic injuries such as to significantly improve individual and public health.

Resuscitation’s Unique Physiology

Resuscitation science differs from more traditional clinical disciplines because impairment involves the entire body after ischemic or hypoxic injury. The inciting events that lead to arrest may be quite different, such as primary ventricular fibrillation in comparison with uncontrolled hemorrhage. However, once circulatory failure is imminent or when it occurs, there is a commonality of pathophysiological responses regardless of the inciting event. In the instance of circulatory shock, multiorgan dysfunction with complex interorgan interactions are life threatening. In settings of cardiac arrest, the predominant target organs are the heart itself and the brain. Accordingly, research in this domain extends from localized to generalized ischemic injury. Resuscitation is performed in a diversity of geographic and physical settings, under critical time pressures and with a diversity of delivery systems. If the risks of permanent injury or fatal outcome are to be mitigated, each of these issues will need to be addressed.

Multiorgan Ischemia and Reperfusion: A Complex Adaptive System

When the blood circulation is arrested due to sudden cardiac arrest or impending circulatory arrest from trauma, it is not merely a localized “big heart attack” or a localized “big stroke” or both at the same time. It is a more general insult to every organ, including the heart and the brain, together with complex adaptive responses at level of cells, tissues, organs, and ultimately the organism. The injured organs also have secondary effects on other organs. For instance, when perfusion of the gastrointestinal tract is impaired, barriers are reduced, allowing bacterial toxins to enter the blood stream. Excesses of lactic acidosis are generated within the liver and in skeletal muscle, which alter acid/base conditions of the entire organism. Injury not only to organs but also to blood vessels triggers the release of mediators, which potentially injure otherwise unaffected tissues and cells. As such, resuscitation involves a “complex biological system” with many “emergent properties” that cannot be predicted from study of individual components. Thus, novel strategies are needed that analyze and integrate data at multiple levels, from DNA to the whole host. This complex interaction of such multiple responses is acknowledged to have important but as yet poorly understood actions, which are reflected in cardiorespiratory and neurological malfunction and adverse outcomes. The complex interplay between the heart, brain, cytokines, coagulation cascade, vasculature, gastrointestinal tract, muscle, and other organs and tissues calls for a comprehensive systems approach by a multidisciplinary team of collaborative researchers who address multi-

organ integrated pathophysiology of injury. Resuscitation researchers should also enlist the support of experts in mathematics, biostatistics, computational biology, functional genomics, computer science, and bioinformatics. Experts must therefore join together to explore complex biological systems in an effort to understand mechanisms and evolve more effective interventions. Current priorities of funding also require an awareness of quality of life and monetary costs.

Stimulating Scientific Advances

The advances in the management of acute myocardial infarction as a discrete organ-based life-threatening crisis have yielded a 3-fold reduction in acute mortality, largely as the result of effective coronary reperfusion strategies. Unfortunately, no comparable advances have as yet been achieved with cardiac arrest or after uncontrolled hemorrhage due to trauma. Dysfunction caused by whole body ischemia and reperfusion is more complex and less well understood than those of local or focal ischemia. Yet there is consensus of the need to actively intervene to interrupt the injurious process, minimize ischemic damage, restore perfusion, and prevent deleterious consequences of reperfusion, if recovery is to be improved. Because interventions are almost always time-critical, the need for early intervention is especially challenging. To the extent that resuscitation science shares domains of scientific medical knowledge with traditional organ-based specialties, including cardiology, neurology, hematology, and surgery, we should promote collaboration with appropriate experts in each of these fields. Unique strategies, drugs, and lifesaving devices are required. A major challenge is the development and validation of animal models on which to elucidate mechanisms and test interventions before clinical studies. A corollary need is for increasing dialogue with the FDA, the Federal Office of Human Protection, and other regulatory agencies to secure the legal and ethical propriety of CPR and trauma research on victims.

Rationale for Optimism: We Can Save More Lives

The consensus of international experts is that we will have substantial improvement in outcomes for victims of cardiac and traumatic arrest, but contingent mainly on augmented research support. The success of early defibrillation made possible by the development of automated external defibrillators is a striking example of a major innovation in resuscitation within the last 10 years. This advance in science and technology has allowed survival in some settings to be increased from a most disappointing 0% to as high as 75%. Nevertheless, this major advance is highly time-limited. It provides the most benefits to victims within the narrow time window of less than 4 minutes after onset of cardiac arrest. We are therefore prompted to search for interventions, which will surmount such a “4-minute barrier.”

Reperfusion injury follows ischemia. Prevention and/or treatment of reperfusion injury may offer opportunities to significantly improve survival rates. Accordingly, better understanding of reperfusion injury in the early post-resuscitation
interval provides a promise for improving outcomes of ischemic injury. For instance, hypothermia and induction of hibernation are examples of potentially promising interventions,\(^{27-35}\) although we recognize potential adverse effects, especially in settings of trauma.\(^{36}\) Hibernating animals tolerate ischemia and reperfusion without injury and therefore represent a potentially valuable model.\(^{37,38}\) Controlled reperfusion with cardiopulmonary bypass after cardiac arrest and/or profound circulatory shock, for instance, provides a potentially important advance.\(^{39-43}\) This novel approach is viewed as promising for victims of prolonged cardiac arrest due to ventricular fibrillation.\(^{44}\) We also recognize immunological options including modulation of the coagulation cascade,\(^{45}\) including monoclonal antibodies to counteract mediators of cell injury and death.\(^{46,47}\)

**Stimulating Advances and Interest in Resuscitation Science**

The PULSE Initiative in the United States and Canada has brought attention to the need for greater support of resuscitation science. The initial meeting of PULSE in June 2000, which included international representation resulted in the following: (1) a more precise definition of the knowledge base and the scope of resuscitation sciences; (2) prioritization of resuscitation research projects; (3) recognition of the need of increased collaboration between laboratory and bedside investigators; (4) a commitment to recruit young researchers to enter the field; and (5) new synergy between federal agencies charged with supporting such research, especially the National Institutes of Health, the Department of Defense, Food and Drug Administration, and the Department of Energy. The experts called for increased momentum, both national and international, to secure initiatives for improving resuscitation outcomes through appropriate support of basic, applied, and clinical research.

**Strategies and Priorities for Resuscitation Research**

The PULSE Leadership Group collated, distilled, and prioritized research initiatives. It carefully identified and classified subjects for priority attention and opportunities for implementation. Eight working groups were convened that considered the following: acute myocardial rescue, neurological preservation, pharmacotherapeutics, ventilatory management, mechanical circulatory adjuncts and bioengineering of new devices, epidemiological initiatives, and trauma care. These groups met over a 2-year period, distilled the results of deliberations in their expert domains, and translated their findings to a preliminary position paper. After the PULSE Workshop convened in June 2000, 200 international experts joined to discuss these position papers. Together with keynote presentations by recognized leaders, the deliberations of the workshop were recorded and delivered to the PULSE leadership group. Continuing evaluation and prioritization by the Leadership Group evolved into a strategic plan. The work product addressed the scientific biological, epidemiological, and engineering issues and the opportunities for implementation pertinent to resuscitation. Five domains of resuscitation science were identified and these included (1) Mechanisms, (2) Pharmacology, (3) Translational Studies, (4) Bioengineering, and (5) Clinical Evaluative Research. Research was prioritized within each of these domains utilizing the designation “A” for projects warranting immediate implementation, “A−” for projects requiring ~1 year for implementation, and “B” for projects that are anticipated to evolve over the next 5 years. The priorities took into account timing that would dovetail with currently available knowledge and technology (see the Table). The Leadership group cited the following categorical projects for priority funding:

**Mechanisms**

1. Hibernation physiology in settings of ischemia and reperfusion (A)
2. Controlled reperfusion (A)

**Pharmacology**

1. Improved understanding of currently used and newly proposed agents in the management of cardiac arrest (A)
2. Inducing blood coagulation at the site of severe hemorrhage (A−)
3. Prevention of diffuse coagulopathies (A−)
4. Minimizing endothelial injury (B)
5. Minimizing parenchymal injury (B)

**Translational Research**

1. Hypothermia (A)
2. Controlled reperfusion (A)
3. Mechanisms of generating greater blood flows during CPR (A)
4. Animal models (A)
5. Induction of hypometabolic states (B)
6. Options for reducing the injurious effects of free radicals (B)

**Bioengineering**

1. New biosensors for detection of critical limitations of blood flows (A)
2. Methods for inducing hypothermia (A)
3. Automated notification of cardiac arrest with a device applied to unconsciousness or traumatically injured victims (A)
4. Vascular access for reperfusion technologies (A)
5. New mechanical devices and methods for securing maximal forward flow during cardiac arrest (A)
6. Gene product sensors (B)
7. Simulation and telemedicine (A)

**Clinical Evaluative Research**

1. Regional, national, and international registries on trauma and CPR (A)
2. Clinical trial networks (A)

(1) Hibernation Physiology in Settings of Ischemia and Reperfusion (A)

The physiology of hibernation offers insights into what may become one of the most important breakthroughs in the treatment of global ischemia. In settings in which oxygen delivery or availability is reduced, ischemic injury is minimized or prevented by reducing the oxygen need both locally.
and systemically. During hibernation, the heart rate decreases to as little as 5% of normal, levels that would be lethal during active states.48,49 Remarkably, no damage occurs during this prolonged “ischemic” state, nor does the cardiac rhythm deteriorate into ventricular fibrillation.50 After arousal and restoration of normal blood flows, the “reperfused” organs and tissue show no evidence of ischemic injury. Potent hibernation signaling molecules, membrane receptors, and intracellular cascades have recently been described, but there is very little insight into these natural protective mechanisms.38,51–54 The value of hibernation in the presence of shock has not as yet been adequately explored and will require research before clinical trials in the setting of trauma can begin. The possibility exists that therapeutically induced hibernation may also minimize both ischemic and reperfusion injuries.37 The development of transient therapeutic hibernation or a “stasis” state wherein injury to human organs would be prevented during ischemic states may have a profound benefit after major injuries associated with critical reductions in vital organ perfusion.55

2. Controlled Reperfusion (A)

As we enter this new century, we still search for the point at which an injured cell transitions beyond the “point-of-no-return” with respect to cell survival.56–59 The rationale of current therapy is to protect injured cells from death; therefore, protecting vulnerable or injured cells on the verge of death is a promising goal of resuscitation therapy. There is recent data to suggest that cells exposed to ischemia and reperfusion could be saved for intervals that are much greater than those that we currently regard as beyond the threshold of reversible cell death.60–62 The concept has been extended to include “controlled reperfusion” and “controlled hypotensive resuscitation” in which the conditions of reperfusion are manipulated to minimize rebleeding and reperfusion injury and to maximize cell recovery.39–44 These concepts are pertinent to preservation of neurons in settings of global brain ischemia, cardiomyocytes for minimizing cardiac ischemic injury, and pneumocytes to prevent respiratory distress syndromes.63–68 In addition, we need a better understanding of vascular mechanisms by which not only the quantity but also the quality of blood flow to organs during ischemia is optimized. We anticipate that controlling reflow to ischemic organs during recovery from ischemia will be beneficial.69 Moreover the physiological interplay between parenchymal cells and the vascular system, including specific triggering events, signaling pathways, oxidant generation, ionic disturbances, inflammatory mediators, and apoptosis in the settings of global ischemia require investigation.57,70–73 The experts recognized that these research objectives are likely to be greatly facilitated by insights gained from advances in understanding of localized injuries due to cancer, coronary heart disease, ischemic and hemorrhagic strokes, and traumatic injuries to organs.

Pharmacology

Molecular medicine, genomics, and proteomics have promise of leading to novel life-saving drugs.16 Recent advances in technology make it possible to determine not only genome-wide changes in transcription and translation induced by circulatory arrest and trauma, but also genotypic variations that alter outcome. The fields of functional genomics and pharmacogenomics will provide an opportunity to model and then test novel approaches to understand adaptations to ischemic injury. The emphasis is placed on functional genomics, as any genomic-based approach must be understood in the larger context of integrative organismal complexity.16 Injury disrupts the function of organs and tissues; coordinated function of these tissues is essential for homeostasis. Accordingly, better understanding the adaptive response requires integration of knowledge at the molecular, cellular, tissue, organ, and whole organism levels. Extracting information from the enormous data sets produced by these highly parallel, genome-wide investigations requires the application of novel analytical tools that query complex adaptive systems.

1. Improved Understanding of Currently Used and Newly Proposed Agents in the Management of Cardiac Arrests (A)

More optimal vasoactive and antiarrhythmic drugs are needed.74 Current guidelines for the administration of epinephrine or more selective α-adrenergic agents, vasopressin, procaine amide lidocaine, and amiodarone are admittedly based on the best available science; however, experts concede that the objective justification for their use is insecure.75 Because these are the drugs that are presently in routine use for the management of cardiac arrest in human victims, the experts regard this research domain as an especially high priority.

2. Inducing Blood Coagulation at the Site of Severe Hemorrhage (A–)

We also recognize the potential value of specific agents that promote blood clotting at the site of hemorrhage during the course of massive blood loss.

3. Prevention of Diffuse Coagulopathies (A–)

Acquired coagulopathies can become life threatening after major body trauma, severe hemorrhage, or surgical operations.76 Intravascular coagulopathies are also observed under diverse conditions of reduced blood flow, especially trauma, hypovolemia of other causes, extreme environmental conditions, sepsis, and cardiac arrest.77 Data suggesting that thrombolytic agents improve cerebral blood flow after cardiac arrest highlight an important role for moderating blood coagulation in these settings.78–80 We especially recognize the importance of searching for methods of prevention and treatment of coagulopathies that accompany hypothermia and/or low blood flow states.

4. Minimizing Endothelial Injury (B)

The endothelium itself is a target during states of ischemic injury and reperfusion.11 Endothelial swelling, capillary plugging, and loss of vascular tone may account for exacerbation of injury of remote organs or cells. There is increasing recognition that the endothelium serves as a critical organ that not only separates the blood from the tissues, but also plays a central role in communication between the organs and vital circulatory elements including coagulation factors. Circulatory arrest and trauma can activate endothelial cells to recruit...
neutrophils, which adhere to the endothelium, activating cytotoxic proteases, and ultimately leading to oxygen-derived free radicals, which further promote the cascade of events responsible for the end-organ damage.

5. Minimizing Parenchymal Injury (B)
In settings in which systemic perfusion failure is primarily due to a local injury, as in the case of acute myocardial infarction or stroke, the option of minimizing parenchymal cell injury is promising. As in the case of myocardial infarction and stroke, reestablishing more normal blood flow constitutes a specific intervention. We further look to opportunities for improved drug delivery to localized sites of life-threatening parenchymal injury.

Translational Research
Increasing evidence suggests the need for better “translational” research and for animal models that more precisely mimic human cardiac and traumatic arrest. Translational research provides the critical link between mechanisms and interventions that develop out of basic science laboratories and that are advanced to preclinical testing. Basic studies addressing mechanism are likely to be fruitful when performed in cell cultures and isolated organs. However, translational research is mandatory before human application. Significant insights into more complex interactions including toxicology only emerge after studies on intact small and large animals. Particular priority should therefore go to translational studies performed by experts in integrative physiology and pharmacology. Institutional support, including Institutional Animal Care and Use Committees and veterinary support services, are required for continued progress in this area.

1. Hypothermia (A)
Among the highest priorities is the expectation that hypothermia after CPR and cardiac arrest will improve outcome. Current data provide optimism that it is protective and relatively free of major toxic or adverse affects.27–35 By contrast, conflicting data on the role of hypothermia in the trauma setting requires additional laboratory evaluation prior to clinical studies. Hypothermia, if sustained for a prolonged time, may produce harmful effects that likely outweigh potential protection.81–83 Emphasis should be placed on determining the mechanism of hypothermic protection while alleviating the potential adverse effects, such as coagulation defects and toxicity. Detailed information concerning the timing, severity, and duration of hypothermia after injury and resuscitation in animal models is needed. Insights are needed to secure more comprehensive understanding of the mechanisms by which hypothermia is protective, especially after prolonged hypoxia. Persuasive preclinical translational studies are a prerequisite for human trials, particularly in the trauma setting.

2. Controlled Reperfusion (A)
Controlled reperfusion is performed with the aid of cardiopulmonary bypass and with the use of a specific perfusate that is demonstrated to be beneficial; as had been demonstrated to be lifesaving in settings of intractable ventricular fibrillation.39–44 The presumption that toxic metabolites contribute to reperfusion injury should be reinvestigated. Optimal procedures for implementation and timing must still be defined.

Modern CPR began with precordial compression to produce forward blood flow in the absence of spontaneous cardiac contraction.84 New techniques and devices that increase the efficacy of closed-chest precordial compression are sought. Not only do we seek methods that increase systemic cardiac output, but agents should be sought to improve microcirculatory flow.78,79 Mechanical devices that promote forward blood flow, including devices that are portable and adaptable for out-of-hospital uses, are of potentially great value.73,85 Nevertheless, the major limitation in implementation of total body perfusion continues to be the as yet limited capability for rapid vascular access.85 We address this issue as a separate priority (vide infra).

4. Animal Models (A)
Realistic small and large animal models of cardiac and traumatic arrest are needed. Further development of small animal models of cardiac arrest, especially in mice, would provide a needed link to recent advances in molecular biology and genetics.86 Further optimization of the large animal models, including genomic characterization, will likewise advance the field. Animal models of cardiac and traumatic arrest in support of the translational research, as cited above, are awaited.

5. Induction of Hypometabolic States Together With the Option of Reducing the Effects of Free Radicals (B)
Additional strategies are needed to induce reduced metabolic rates such as hibernation and hypothermia. These are assumed to be protective in that they reduce the progression of ischemic injury including cell death. A separate role for defining the effects of free radicals generated during ischemia states are needed and their relationship to reperfusion injury, to the activation of signaling molecules, and to the release of mediators of cell injury and cell death deserve further investigation. Translational studies, which improve our understanding of these basic mechanisms, should be pursued.

Bioengineering
Bioengineering advances are needed, including the development of defibrillators, electrical and mechanical monitors of cardiopulmonary function, airway devices, and vascular access technologies. EMS systems have impacted favorably on the care of the critically ill and injured. Both fundamental research in biological engineering and support of research and development for improved instrumentation is sure to advance outcomes of resuscitation. We therefore request a meaningful partnership between bioengineering and both basic and applied resuscitation sciences. Immediate priorities include the following:

1. New Biosensors for Detection of Critical Limitations of Blood Flows (A)
We currently lack biosensors with which to quantify blood flow during CPR—a critical challenge. We likewise need the ability to rapidly diagnose anatomic injury during out-of-
hospital resuscitation of trauma victims. The guidelines for resuscitation have traditionally been written so that algorithms provide the sequence of interventions, but with little objective feedback and documentation of the victim’s response or lack of response. Real-time measures indicative of cellular oxygen concentrations and/or high-energy phosphates, concentrations of hydrogen ions, calcium, and carbon dioxide are all indicative of the severity of tissue hypoxia. Such biosensors are likely to advance clinical management. Another high priority is the quantification of cerebral blood flow and/or rapid markers of cerebral injury, which would more competently guide the management of traumatic brain injury and hypoxic encephalopathies.

2. Methods for Inducing Hypothermia (A)
Where the beneficial effects of hypothermia are proven, a new methodology is needed for instituting rapid whole body or vital organ regional cooling. It is especially important in the pre-hospital setting, where the protective effects may be great.

3. Devices for Remote Notification and Improved CPR and Trauma Care (A)
Sensors, which serve to detect and alert, are sought. Such detectors would serve as early warning devices, not unlike smoke detectors. They could have the ability to integrate and analyze real-time physiological and metabolic data and would promote documentation of pre-hospital interventions and the development of effective decision assisting devices. It is anticipated that remote notification devices will be especially useful for responding to life-threatening events that are unwitnessed. We recognize the option for “smarter” defibrillators, smaller and less costly, and including more comprehensive prompting and communication with professional medical providers.

4. Vascular Access (A)
A major restraint in the clinical management of cardiac arrest and life-threatening traumatic injuries is the capability for securing rapid vascular access. Vascular access is a prerequisite for prompt drug delivery during resuscitation, for cardiopulmonary bypass, and for other invasive vascular procedures, including angioplasty and selective control of arterial hemorrhage.

5. New Mechanical Devices and Methods for Securing Maximal Forward Flow During Cardiac Arrest (A)
In the past decade, a number of elaborations of conventional manual chest compression have been investigated. These new techniques include active compression-decompression, intermittent abdominal compression, devices that provide both active compression/decompression and abdominal compression, circumferential compression utilizing either a vest or a belt, and invasive methodologies including both proximal aortic and distal aortic balloon occlusion. Percordial compression devices that are pneumatically or hydraulically powered have also been described. Each of these concepts deserves vigorous testing and opportunities for refinements.

6. Gene Product Sensors (B)
Multigene product sensors provide a promising research tool for improved understanding of the biochemical and metabolic cascades that are activated during ischemia and reperfusion. The capability of identifying early response gene and their products, genetic polymorphisms associated with survival, and other genetic products deserves thorough investigation.

7. Simulation and Telemedicine Technologies (A—)
The use of sophisticated human patient simulators for training and testing will allow a reproducible learning environment with consistent standards. Integration of the virtual skill stations with realistic tactile properties (ie, haptics) will further the usefulness of successive generations of human simulation. The integration of real physiological data accumulated in the field will improve the realism of the simulated environment. Use of telecommunication currently allows reliable verbal links between advanced centers and the field for immediate resuscitative care; however, newer telemedicine technology is hoped to improve the scope of this activity. Future possibilities include teaching, monitoring, and interpretation of advanced diagnostic techniques and therapeutic interventions utilizing high-bandwidth video technology. Technology and devices could be utilized for the continuous pre-hospital collection of various physiological data. These data may be analyzed and integrated into decision assisting devices and utilized to document the effectiveness of new methods of rapid vascular access, hemorrhage control, cerebral protection, and optimal methods of resuscitation and metabolic manipulations.

Clinical Evaluative Research
A critical need is the dissemination of new clinical knowledge of the effectiveness of interventions. Accordingly, we favor supporting the capacity for conducting large simple clinical trials of promising resuscitation interventions.

1. Regional, National, and International Registries on Trauma and CPR (A)
Regional and national registries provide databases, which translate into improved understanding of current and potentially effective new practices. Trauma care would especially benefit from a uniform case definition to promote data comparability between regions and the collection of objective data on causes, pathologies, treatments, and outcomes. Although some registries have been established, a national database is proposed to enhance the statistical power of the data acquired and to include information about pre-hospital processes and outcomes. A comparable countrywide registry for CPR would also provide useful data, including highly variable geographic survival rates. Registries also define educational and training needs.

2. Clinical Trial Networks (A)
The conferees especially emphasized the need for prompt evaluation of promising new interventions derived from translational research and phase II clinical trials. Cardiac, asphyxial, and traumatic arrest should each be addressed and included in high-quality randomized controlled and appropriately powered trials. Both effectiveness and cost data should be collected.

Clinical trials are demanding because of major ethical, organizational, and fiscal constraints. However, randomized
clinical trials provide the only option for establishing secure guidelines and corresponding improvements in practices. Specific subjects for whom very early trials are recommended include the following: (1) early use of amiodarone; (2) optimizing bystander CPR with modified ventilation/compression methods and sequences; (3) optimal fluid resuscitation strategies for trauma patients; (4) improved methods of hemorrhage control; and (5) comparative trials of curricula of both lay and professional education. Additional interventions that are promising future candidates for clinical trials include (1) optimal vasopressor therapy during cardiac arrest and (2) rapid induction of moderate hypothermia during cardiopulmonary arrest. A well-supported and directed clinical trial network, which will ensure appropriate pilot studies and take responsibility for organizing, coordinating, and monitoring controlled trials, is strongly recommended. Given ongoing concern for the cognitive outcomes of survivors, a detailed neuropsychological assessment of survivors should be an important substudy of one or more of these clinical trials. A leadership group with appropriate representation of medical, epidemiological, and scientific experts and community representatives who are specifically charged to ensure appropriate waiver of informed consent must be identified to guide clinical trials.

Specific Recommendations to NIH for Implementation of the PULSE Strategic Plan

1. Develop a National Center for Resuscitation Research represented by a broad-based initiative among institutes and partnering with other government agencies. The National Heart Lung Blood Institute (NHLBI), National Institute of Child Health and Human Development (NICHD), National Institute of General Medical Sciences (NIGMS), and National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health, the Food and Drug Administration (FDA), and the Department of Defense (DOD) have already demonstrated effective collaboration and support of the PULSE Initiative. These across-institute and -agency collaborations with priority focus on resuscitation would be encouraged to identify and recruit other agency participation including the Department of Energy (DOE) and the new Bioengineering Institute.

2. Recognize the need for and implement programs that prioritize support for resuscitation research. This should include grants and/or contracts as support to consortia of investigators who collaborate throughout the spectrum from basic science, applied and bioengineering research, and clinical investigations and preferably all three. We specifically encourage support of shared core facilities.

3. Prioritize development of a multicenter network in support of clinical trials. The South West Oncology group (SWOG) serves as an example of successful implementation for oncology. Comparable benefits are certain if a resuscitation clinical trials network, preferably international in scope and participation, were available. To the extent possible, both basic and translational research deserve priority consideration. Joint funding from both government and industry will likely be necessary to support the network.

4. Prioritize specific programs of support for the development of strategies and devices in support of biosensor technologies to guide diagnosis, monitoring, and response to resuscitation interventions.

5. Support development and maintenance of registries of clinical cases on resuscitation. Current registries should be expanded to include trauma and cardiac arrest, especially in the pre-hospital/EMS setting.

6. Extend education and training opportunities for both laboratory and clinical researchers on resuscitation including fellowships and developmental support for junior faculty. The critical shortages of researchers on trauma, emergency medicine, bioengineering, critical care, and nursing should be addressed. Focused training grants and institutional research training awards in resuscitation medicine are recommended.

7. Ensure that either organize panels of qualified experts on resuscitation and/or ensure the appropriate inclusion of reviewers from such panels on the study sections to which applications are directed. Clinical investigators who have experience and expertise in the conduct of clinical trials, including federal regulations, should be enlisted.

8. Direct appropriate agencies of government to promote public education and enhance public awareness of acute life-threatening conditions and therapies and to acknowledge the need of support for research and development on resuscitation. NIH would best take a leadership role in addressing the current state of resuscitation research and identifying opportunities for sponsoring novel initiatives. We also propose enhanced internal communication within NIH and call attention to the availability of the PULSE leadership to serve on the institute councils.

References


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