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ever than 8% of adult out-of-hospital cardiac arrest (OOH-CA) victims survive to hospital discharge despite public education of event recognition, early notification of 9-1-1, bystander cardiopulmonary resuscitation, automated external defibrillator (AED) use, therapeutic hypothermia, and improvements in emergency medical service delivery.1 Densely populated urban areas such as New York, NY, and Chicago, Ill, where a large number of cardiac arrests occur, report even lower (1.4% to 2%) survival rates.2-3 Unlike other areas of cardiovascular health such as myocardial infarction, which has demonstrated a 3-fold decrease in acute mortality,4 the improvements in outcome from OOH-CA have remained modest over the last 25 years.5

Is this dismal survival and lack of progress a result of the biological lethality of the condition, or has inadequate research been done to define its pathogenesis, pathophysiology, and prevention and the optimal implementation of effective treatments? OOH-CA is obviously a life-threatening condition, yet it is a “treatable disease” in the sense that medical interventions can improve survival significantly.6-9 Moreover, a nearly 500% difference in survival rates exists across communities in the United States, suggesting that variability in the quality of resuscitation care is driving large differences in community survival rates.9 Collectively, these data suggest the potential for a major improvement in community survival rates that could save tens of thousands of lives. So where is the problem?

Improving care and survival requires a commitment to sustained, high-quality, basic scientific and clinical research. Despite the devastating public health consequences of OOH-CA, the randomized clinical trial (RCT) base from which evidence-based resuscitation guidelines are derived is limited compared with that used to derive evidence-based guidelines for other cardiovascular diseases. Table 1 lists the number of MEDLINE English language citations of resuscitation RCTs compared with ST-elevation myocardial infarction,10,11 stroke,12-14 or chronic heart failure.15-17 The last 3 guidelines are supported in community survival rates.9 Collectively, these data suggest the problem is varied (Table 2), there are 25 to 86 times the number of published randomized controlled trials per 10 000 deaths per year for the latter cardiovascular versus resuscitation guidelines.

An important contributor to the mismatch between the published science base and public health burden of these cardiovascular conditions is the relative paucity of cardiac arrest clinical trials until recently. Before 2000, the year of the National Institutes of Health (NIH) –sponsored Post-Resuscitative and Initial Utility in Life Saving Efforts (PULSE) conference,8 which identified the need to fund more multidisciplinary basic science and translational research on major trauma and cardiac arrest, there were only 3 RCTs funded by the NIH: 2 Brain Resuscitation Clinical Trials (BRCT I and II), which failed to show improved neurological outcome from relatively late administration of promising drugs initiated up to several hours after resuscitation,18,19 and the Public Access Defibrillation (PAD) trial, which documented a doubling of survival from OOH-CA occurring in public places when laypersons were trained and equipped to use AEDs compared with results achieved when laypersons could just call 9-1-1 and perform cardiopulmonary resuscitation.7

In 2004, the NIH/National Heart, Lung, and Blood Institute (NHLBI) funded the Resuscitation Outcomes Consortium (ROC) with a mission to conduct clinical effectiveness trials on OOH-CA and major traumatic injury. Additional ROC support is provided from the Institute of Circulatory and Respiratory Health of the Canadian Institutes of Health Research, the American Heart Association, the US Army Medical Research and Materiel Command, the National Institute of Neurological Disorders and Stroke, Defense Research and Development Canada, and the Heart and Stroke Foundation of Canada. In addition, NIH has funded the Home Automated External Defibrillator (HAT) Trial in which access to a home AED did not significantly improve overall survival compared with reliance on conventional resuscitation methods in anterior wall myocardial infarction survivors who were not candidates for implantation of a cardioverter-
defibrillator. However, these few clinical resuscitation trials are dwarfed both numerically and by total dollars invested by clinical trials in myocardial infarction, heart failure, and stroke. The lack of outcome studies additionally suggests that inadequate translational research is being performed, including smaller-scale clinical trials to identify promising avenues for definitive trials.

The gap between cardiac arrest/resuscitation and other common life-threatening cardiovascular conditions is not only for clinical trials but also for NIH-funded research across the translational continuum from basic science to implementation studies. Table 2 lists the total number of combined basic science and clinical research projects funded by the NHLBI from 1985 to 2009 as obtained from the NIH Research Portfolio Online Reporting Tool for each condition. Once again, there is a huge disparity in the number of projects funded dealing with cardiac arrest and resuscitation compared with myocardial infarction, heart failure, and stroke. When the public health mortality burden of the disease is considered, there are 35 to 53 times the number of published randomized controlled trials per 10,000 deaths per year for the latter cardiovascular guidelines compared with that of cardiac arrest and resuscitation. Although it can be argued that the NIH is simply not receiving enough high-quality research proposals on cardiac arrest and resuscitation, it is also true that a history of successful funding of applications for definitive trials.

Another important consideration is that a large number of clinical trials on myocardial infarction, stroke, or chronic heart failure are funded by nongovernmental entities, particularly large pharmaceutical and/or cardiovascular device manufacturers. Perhaps because there has been a relative paucity of funded basic science research on resuscitation compared with these other cardiovascular conditions, very few novel, patent-protected drugs are in the resuscitation “pipeline.” Pharmaceutical/device manufacturers have been unwilling and/or unable to fund multimillion-dollar clinical trials on patent-unprotected drugs and devices commonly used in resuscitation (eg, atropine, epinephrine, sodium bicarbonate, lidocaine, external pacemakers). The few pharmaceutical industry-sponsored resuscitation trials that exist have been funded or powered insufficiently to demonstrate improvement in survival to hospital discharge and/or neurological outcome. In contrast, there are many published, high-quality, manufacturer- and NIH-sponsored clinical trials studying implantable cardioverter-defibrillators, which are relatively high-cost, patent-protected, surgically implanted devices used for primary or secondary prevention of sudden cardiac death caused by ventricular tachyarrhythmias. Unfortunately, primary prevention with implantable cardioverter-defibrillators is of limited value because the majority of cardiac arrests occur in individuals with undiagnosed disease, mostly those profiled to be at low absolute risk based on conventional risk markers. Because there is no “pharmaceutical deep pocket,” it is even more critical for the NIH to assume primary responsibility for resuscitation research funding.

OOH-CA claims the lives of an estimated 310,000 Americans each year, a loss of life equivalent to that caused by a 9-1-1 World Trade Center attack on the United States every 3 days. Despite important progress on increasing awareness and recent initiation of limited NIH-funding directed toward the problem, not enough is being done to make basic science and clinical trials funding a serious priority. The funding commitment by the NIH and industry is not commensurate with the impact of cardiac arrest on the public’s health or the likelihood that significant improvements in survival are within our grasp. This is particularly troubling given the 500% variation in community survival from cardiac arrest compared with only 25% to 50% variation in community survival for acute myocardial infarction. Cardiac arrest survival rates suggest that significant improvements can be made in nearly every community that would result in the

Table 2. Number of Research Projects Funded by the National Heart, Lung, and Blood Institute From 1985 to 2009

<table>
<thead>
<tr>
<th>Terms Searched</th>
<th>Funded Studies, n</th>
<th>Funded Studies per 10 000 Deaths per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>6886</td>
<td>157 000</td>
</tr>
<tr>
<td>Stroke</td>
<td>4403</td>
<td>150 000</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9919</td>
<td>284 000</td>
</tr>
<tr>
<td>Heart arrest and resuscitation</td>
<td>257</td>
<td>310 000</td>
</tr>
</tbody>
</table>

Limits that were applied to the searches: humans, clinical trial, randomized controlled trial, and English. “Clinical trials” indexing term was introduced in 1965; “randomized controlled trials” indexing term was introduced in 1990.
prevention of tens of thousands of premature deaths each year. Thus, resuscitation from cardiac arrest is a remarkably promising intervention that should be included in the new US initiative on relative effectiveness research.

We strongly commend NHLBI for leading the way in the last decade to recognize the gap between the public health importance of cardiac arrest and the science base needed to support improved care, for organizing the PULSE conference, for funding the Public Access Defibrillation and Home AED trials, and for establishing the ROC. Each of these initiatives is a major step in the right direction, and they are particularly noteworthy because cardiac arrest, resuscitation, and trauma do not have a traditional “home institute” within the NIH organizational structure. These efforts are necessary but only first steps in a long, needed journey.

We believe it would be productive for the NIH to explore mechanisms to end the vicious cycle in which a small number of grant requests leads to little funded research on cardiac arrest and resuscitation. Such a dilemma might be addressed by creating a special area of project interest with significant targeted funding for basic science and translational clinical research similar to the NHLBI’s highly effective Myocardial Infarction Research Unit and Ischemic Heart Disease Specialized Centers of Research programs that began in the 1970s and 1980s. The NHLBI combined basic and clinical research centers have also had a remarkable impact on heart failure. Since the 1970s, these targeted programs have played a major role in reducing the acute myocardial infarction mortality rate almost 10-fold (from >40% to <4%) and heart failure by at least 30%. We believe it is time for a similar focus targeting OOH-CA.

Disclosures
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References


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