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Increasing National Institutes of Health Funding for Cardiac Arrest Research

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It is a truth universally acknowledged that an agency in possession of funds must be in need of a worthy cause. In this issue of *JAHA*, Coute et al[1] review the funding record of the National Institutes of Health (NIH), the largest funder of biomedical research in the world, to assess its investment in cardiac arrest research. These authors used a very systematic and replicable strategy to sort grants. It appears that about $29 million per year of the $30 billion total budget was invested by NIH specifically to study cardiac arrest. Cardiac arrest has huge public health impact: This syndrome accounts for 1 death in 6 and is the third leading cause of death in the United States.[2] The explicit message is that cardiac arrest research is worthy of more funding than it has received in the past and that NIH should increase the investment in this research. This conclusion contains several assumptions that we should examine.

First, are the results accurate? The authors used a reasonable approach to measure direct investment in cardiac arrest research. Cardiac arrest is the interruption of heart pumping activity that requires mechanical support or CPR. Multiple methods for CPR exist presently, including manual chest compression, mechanical compressions, and extracorporeal life support. Many patients die because these techniques do not restart the heart. The authors identified grants using the NIH public database and included grants based on their abstracts that specifically addressed cardiac arrest or CPR. When CPR does restore heart function, patients may have dysfunction in multiple organ systems as a result of ischemia–reperfusion,[3] and injury to the brain accounts for the majority of post-CPR mortality.[4,5] To study this particular situation, the authors also included projects that studied global brain ischemia. This approach seems very specific for identifying grants addressing cardiac arrest.

Second, is it accurate that grants that do not explicitly mention cardiac arrest are not addressing this syndrome? This assumption may be overly simplistic because cardiac arrest is a situation and a final common pathway for death in many diseases. In fact, would any research that reduces mortality from a given disease indirectly prevent sudden cardiac arrest? Research that improves survival in coronary artery disease, respiratory failure, drug overdose, or bleeding would all reduce or delay the incidence of cardiac arrest for an individual. Similarly, post–cardiac arrest patients are a specific subset of critically ill patients with cardiogenic shock, respiratory failure, and organ dysfunction. Perhaps any research on these situations is, in fact, also "cardiac arrest related." The present analysis may not be sensitive for finding all of these projects. Prospective studies asking whether work is relevant to cardiac arrest may be a more sensitive way to ask this question, much in the same way that we ask for American Heart Association grants if a project is "stroke related."

Third, is cardiac arrest really more important than other situations? Every investigator, physician, patient, and group does and should advocate for more research about the particular problem at hand; however, the general public and policy makers seem to underestimate the high burden of mortality from cardiac arrest. In public discussion and media, sudden death is often referred to as a "massive heart attack," confusing the syndrome with other heart disease. For surviving families, sudden death may be perceived as "dying naturally." Perhaps sudden death is so common in our society that the public assumes it is natural. Out of compassion, medical professionals are loath to correct this perception or to suggest that an individual death might have been preventable. Most regrettably, patients for whom resuscitation is not effective do not survive long enough to become advocates for more research on their disease. Previous reviews noted that the amount of research on resuscitation is low relative to the public health impact of cardiac arrest.[6] The Institute of Medicine recommended that efforts begin to

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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increase public awareness that cardiac arrest is a specific syndrome and is treatable.[7] The data from Coute et al help raise this awareness.

Fourth, is the amount of funding or the number of grants an appropriate metric of investment? Increasing the volume of work does not necessarily increase the quality. In addition, work that is impactful need not be expensive. Sometimes very small experiments can alter fundamental assumptions in a field. A frustrating example of the complex relationship between volume and impact is the hunt for neuroprotective drugs. NIH and industry invested billions of dollars over the past few decades to develop agents that will protect neurons during various brain injuries.[8] Despite this, no agent demonstrated efficacy in human disease.[9] The gain in basic scientific knowledge has been tremendous. Nevertheless, National Institute of Neurological Disorders and Stroke (NINDS) examined this track record and created the STAIR (Stroke Therapy Academic Industry Roundtable) criteria to select more focused research for clinical trials.[10] For cardiac arrest research, perhaps we should advocate for similar judicious investment by NIH rather than simply more.

Fifth, can NIH alter its funding priorities? A cornerstone of NIH has been the support of investigator-initiated research. Peer review helps prioritize the applications received, and the various institutes and centers at NIH distribute the available funds to the highest priority applications. The portfolio of extramural research should reflect the applications that are submitted to NIH. A deficit of cardiac arrest research probably reflects a shortage of applications in this domain.

NIH can and does encourage applications toward high-priority diseases or problems. Targeted requests for applications stimulate investigators to submit in a particular area, and set-aside funds can create a stampede of applications. An actionable step would be for various institutes and centers to publish requests for applications specifically about cardiac arrest as it relates to their mission. Cardiac arrest, which most often starts with heart arrest (National Heart, Lung, and Blood Institute [NHLBI]), results in brain injury (NINDS), multiple organ failure (National Institute of General Medical Sciences), and systemic inflammation (National Institute of Allergy and Infectious Diseases); requires extensive rehabilitation, multidisciplinary care (National Institute of Nursing Research), and devices and imaging (National Institute of Biomedical Imaging and Bioengineering); and preferentially affects older persons (National Institute of Aging), minorities (National Institute on Minority Health and Health Disparities), and persons with genetic risk (National Human Genome Research Institute, Eunice Kennedy Shriver National Institute of Child Health and Human Development), should be in the portfolio for almost every institute or center.

Sixth, are the barriers for investigator-initiated cardiac arrest research internal or external to NIH? Factors aside from the availability of funds may discourage investigator-initiated research on cardiac arrest. These barriers include the logistical, conceptual, and design difficulties of research on this syndrome.

In clinical cardiac arrest research, logistical difficulties include multiple organ involvement, multiple specialists involved with each patient, different locations of treatment (out-of-hospital, emergency department, intensive care unit, rehabilitation facilities), and distribution of patients at many different hospitals with varying capacities. Conceptual difficulties include heterogeneity of the patient population, lack of validated outcome measures, lack of accepted surrogate outcomes, and huge variability in background clinical care. Design difficulties include the need to account for the interaction of multiple interventions and for informative censoring (withdrawal of life support prior to reaching an outcome). In addition to these issues, cardiac arrest patients are acutely ill and usually unconscious, requiring studies to obtain consent from distraught families or exception from informed consent using complex approval processes.

In basic cardiac arrest research, logistical difficulties include need for prolonged intensive care in realistic animal models, desirability of large animal models over rodents for modeling organ interactions in humans, and difficulty of accounting for underlying diseases that cause cardiac arrest. Conceptual difficulties include the facts that singular mechanisms are hard to evaluate when every organ system is affected by cardiac arrest, that anesthetics that are not used for humans must be used in animal studies, and that simple geometric differences between species influence important outcomes (eg, brain herniation, drug distribution, chest compression depth, ventilation–compression relationships). Design difficulties include variability in results and specific techniques between different laboratories, absence of multilaboratory networks, and paucity of standardized laboratory models.

Given these complexities, a shortage of qualified or sufficiently motivated investigators partly explains why there are not more applications and more grants at NIH for cardiac arrest research. An actionable item for NIH would be to invest more in training to address these complexities. The PULSE (Postresuscitative and Initial Utility in Life Saving Efforts) initiative in 2000 resulted in a number of K-series awards related to resuscitation.[11] Some of those investigators are among the current project grantees described by Coute et al, demonstrating the return on investment for early career support.

Another actionable item for NIH would be to create research networks that can gain experience with these complexities. The Resuscitation Outcomes Consortium (ROC) was an excellent example of such an investment by NHLBI from 2004 to 2015. ROC conducted 12 randomized controlled

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trials and dozens of cohort studies and advanced the clinical study of cardiac arrest. Coute et al note the impact of ROC on the funding portfolio. NIH is investing again in an emergency trial network (SIREN [Strategies to Innovate Emergency Care Clinical Trials Network]), which has a broader mission than ROC but that can support clinical cardiac arrest research. A preclinical research network, which could standardize laboratory investigations in resuscitation and provide rapid replication of single-laboratory findings, would be an innovative experiment in this space.

In conclusion, is cardiac arrest research a worthy cause? Absolutely. Given more resources, NIH should fund more of every type of research. As a society, we have limited resources and must decide how to prioritize the distribution. It is dangerous to suggest that we should shift funding away from other meritorious work toward cardiac arrest. Instead, we should make effort to increase meritorious cardiac arrest research.

Specific actions by NIH might shift the portfolio to address this major public health problem. Cardiac arrest–specific requests for applications, fostering of research networks, and investment in training of early career investigators are key. We also might encourage all project applications to more explicitly identify their relevance and impact on the leading causes of death. In return, the community of investigators should embrace complex and cross-disciplinary research, create centers and networks with expertise in resuscitation research, agree on common models and protocols, and advocate for a culture of research in acute critical illness. Research is intended to solve problems, and it is very valuable for Coute et al to examine how we currently invest in research on one of our largest problems.

Disclosures

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References

1. Coute RA, Panchal AR, Mafer TJ, Neumar RW. National Institutes of Health–funded cardiac arrest research: a 10-year trend analysis. *J Am Heart Assoc*. 2017;6:e005239. DOI: 10.1161/JAHA.116.005239.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38–e360.
3. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, Kern KB, Laurent I, Longstreth WT Jr, Merchant RM, Morley P, Morrison LJ, Nadkarni V, Peberdy MA, Rivers EP, Rodriguez-Nunez A, Sellke FW, Spaulding C, Sunde K, Vanden Hoek T. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation*. 2008;118:2452–2483.
4. Callaway CW, Schmicker RH, Brown SP, Albrich JM, Andrusiek DL, Aufderheide TP, Christenson J, Daya MR, Falconer D, Husa RD, Idris AH, Ornato JP, Rac VE, Rea TD, Rittenberger JC, Sears G, Stiell IG; ROC Investigators. Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:657–663.
5. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Med*. 2004;30:2126–2128.
6. Ornato JP, Becker LB, Weisfeldt ML, Wright BA. Cardiac arrest and resuscitation: an opportunity to align research prioritization and public health need. *Circulation*. 2010;122:1876–1879.
7. Institute of Medicine of the National Academies. *Strategies to Improve Cardiac Arrest Survival: A Time to Act*. Washington, DC: National Academies Press; 2015.
8. O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1026 experimental treatments in acute stroke. *Ann Neurol*. 2006;59:467–477.
9. Ginsberg MD. Neuroprotection for ischemic stroke: past, present and future. *Neuropharmacology*. 2008;55:363–389.
10. Stroke Therapy Academic Industry Roundtable (STAIR). Recommendations for standards regarding preclinical neuroprotective and restorative drug development. *Stroke*. 1999;30:2752–2758.
11. Becker LB, Weisfeldt ML, Weil MH, Budinger T, Carrico J, Kern K, Nichol G, Shechter I, Traystman R, Webb C, Wiedemann H, Wise R, Sopko G. The PULSE initiative: scientific priorities and strategic planning for resuscitation research and life saving therapies. *Circulation*. 2002;105:2562–2570.

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