

# Stop Randomizing All Cardiac Arrests

**T**he field of resuscitation science is characterized nearly uniformly by failed clinical trials: be it sodium bicarbonate, epinephrine at low or high dose, vasopressin, continuous or interrupted chest compressions, temperature management, antiarrhythmic drug use, or devices to augment perfusion, none has been shown convincingly to be of value.

Nearly all of these large expensive trials included victims of cardiac arrest who met entrance criteria and received efforts to resuscitate to the point in time of the intervention. In many of these trials, a subgroup appears to have greater survival in 1 of the arms of the study. Those subgroups are often patients with likely better survival because the arrest is witnessed and a higher frequency of initial shockable rhythm is present. We are then prone to believe the correctness of the benefit in the subgroup and approach guidelines for treatment with these subgroups in mind.

An extensive review and cautionary note on the risks of subgroup analysis when the overall result is null, and the risk of believing borderline statistically significant overall results, has been published recently by Pocock and Stone.<sup>1</sup> Even recognizing these concerns, I predict, recent clinical trial subgroup differences will haunt cardiopulmonary resuscitation guideline committees going forward. One example is the recently published study<sup>2</sup> of amiodarone, lidocaine, and placebo in refractory ventricular tachycardia or ventricular fibrillation. The overall result showed no statistically significant difference between the individual drugs and placebo, but for the more optimistic subgroup of witnessed cardiac arrest, both drugs were significantly better than placebo. Will the guideline be Class IIb (may or might be reasonable), Class IIa (can be useful or is reasonable), or Class I (is recommended)?

A similar plea to mine, focused on not randomizing patients with an initial rhythm of asystole, was published by Kreuziger and Wenzel<sup>3</sup> in 2009. As they point out, rarely is an asystolic arrest going to respond to treatment. Sinus arrest and heart block are rare and respond frequently to chest compression. Since the time of that publication, the issue of nonshockable rhythms has become even more important. The frequency of initial pulseless electric activity (PEA)<sup>4</sup> arrests has increased remarkably. Recent epidemiological studies have identified initial shockable arrests (pulseless ventricular tachycardia or ventricular fibrillation) as occurring in nearly 25% of all arrest victims.<sup>4</sup>

Appropriately, clinical trials in resuscitation have focused on factors that appear to show benefit in experimental large animal models. The vast majority of these models are acute shockable arrests with <10 minutes of untreated ventricular fibrillation. Even in excellent emergency medical service systems, PEA arrest survival is far below that with initial shockable rhythm. Rarely has PEA arrest been modeled in large animals. We just do not know what to try. Major ambiguity surrounds the etiology of PEA arrest. Pathology studies have been limited, but some suggest that pulmonary embolism<sup>4</sup> is frequent. If correct, management would likely be quite specific to that etiology.

Myron L. Weisfeldt, MD

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

**Correspondence to:** Myron L. Weisfeldt, MD, Department of Medicine, Johns Hopkins University, 750 E. Pratt St, Baltimore, MD 21202. E-mail mlw5@jhmi.edu

**Key Words:** arrhythmia  
 ■ cardiopulmonary resuscitation  
 ■ heart arrest ■ trials

© 2016 American Heart Association, Inc.

Another important distinction between animal models of ventricular tachycardia or ventricular fibrillation arrest and clinical practice is the ability to give drugs intravenously and centrally in the circulation as soon as resuscitation has begun. Even in well-performing emergency medical service systems, the time delay to administer any drug is substantial. Delays to giving drugs are commonly 7 to 20 minutes after the onset of resuscitative efforts. In the animal laboratory, potentially no delay exists. This problem seeks a solution in the clinical setting.

Cardiac arrests that occur in public places are more frequent in individuals without known severe cardiac disease because they are out and about. It is not surprising that initial shockable arrest is far more frequent in public locations, particularly if the onset of the episode is witnessed. Data from the Resuscitation Outcomes Consortium<sup>5</sup> document that most arrests (>60%) that are witnessed in a public location are initial shockable arrest.

In contrast, in the home, only 35% of witnessed cardiac arrests are shockable.<sup>5</sup> Initial shockable cardiac arrests witnessed either at home or in public are much more relevant to the experimental animal model than initial asystole or PEA arrest. Randomizing all cardiac arrests victims also dilutes the potential benefit because of the inclusion of elderly residents of nursing homes, patients with severe chronic heart disease living at home, and those with other chronic and severe comorbidities whose prognosis is poor even before their arrest.

In summary, based on the animal model experiment results, who can we conclude are the patients who should be randomized in arrest trials, and what will be the potential impact? The answer would appear to be witnessed shockable arrests and not initial PEA or asystole arrests.

Although only 14% of all out-of-hospital cardiac arrests are initial shockable arrests witnessed by a bystander, 14% of 350 000 out-of-hospital cardiac arrests per year in the United States would be 49 000 arrests per year. These patients could potentially be entered into what I would term focused clinical trials. Currently,  $\approx$ 30% of these patients survive to leave the hospital alive with good neurological function. An effective drug or intervention limited to this population by randomizing only these patients could lead to impressive improvement in survival. If survival were increased from 30% to 37.5%, then  $\approx$ 3700 lives would be saved every year through the improved treatment of this subgroup. If survival doubled, then 14 700 lives would be saved per year. Once shown in a primary randomized group to improve survival in witnessed shockable events, the intervention might be extended to the larger group of all shockable arrests where greater survival benefit might be achieved.

From a clinical trials point of view, to have 80% power for an increase in survival from 30% to 37.5% (25%) would require 623 patients in each group for a 2-arm

study. If the same improvement were observed in all cardiac arrests, to have 80% power for an increase in survival from 10% to 12.5% (also 25% increase) would require 2507 patients in each group for a 2-arm study.

Current technology would allow for rapid identification of this subgroup with shockable arrests. Even if there were no bystander-placed AED on the patient, phone and stand-alone devices that are placed on the chest will immediately identify shockable rhythm even before the emergency medical service places leads on the chest. Thus, subgroup identification and randomization can be quickly performed. A question about “witnessed” should be rapidly answered, and after shockable rhythm is determined the study begins.

## DISCLOSURES

None.

## AFFILIATIONS

From Department of Medicine, Johns Hopkins University, Baltimore, MD.

## FOOTNOTES

*Circulation* is available at <http://circ.ahajournals.org>.

## REFERENCES

1. Pocock SJ, Stone GW. The primary outcome fails: what next? *N Engl J Med*. 2016;375:861–870. doi: 10.1056/NEJMr1510064.
2. Kudenchuk PJ, Brown SP, Daya M, Rea T, Nichol G, Morrison LJ, Leroux B, Vaillancourt C, Wittwer L, Callaway CW, Christenson J, Egan D, Ornato JP, Weisfeldt ML, Stiell IG, Idris AH, Aufderheide TP, Dunford JV, Colella MR, Vilke GM, Brienza AM, Desvigne-Nickens P, Gray PC, Gray R, Seals N, Straight R, Dorian P; Resuscitation Outcomes Consortium Investigators. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med*. 2016;374:1711–1722. doi: 10.1056/NEJMoa1514204.
3. Kreutziger J, Wenzel V. Overcoming frustration about neutral clinical studies in cardiopulmonary resuscitation. *Resuscitation*. 2009;80:723–725. doi: 10.1016/j.resuscitation.2009.04.028.
4. Myerburg RJ, Halperin H, Egan DA, Boineau R, Chugh SS, Gillis AM, Goldhaber JL, Lathrop DA, Liu P, Niemann JT, Ornato JP, Sopko G, Van Eyk JE, Walcott GP, Weisfeldt ML, Wright JD, Zipes DP. Pulseless electric activity: definition, causes, mechanisms, management, and research priorities for the next decade: report from a National Heart, Lung, and Blood Institute workshop. *Circulation*. 2013;128:2532–2541. doi: 10.1161/CIRCULATIONAHA.113.004490.
5. Weisfeldt ML, Everson-Stewart S, Sitlani C, Rea T, Aufderheide TP, Atkins DL, Bigham B, Brooks SC, Foerster C, Gray R, Ornato JP, Powell J, Kudenchuk PJ, Morrison LJ; Resuscitation Outcomes Consortium Investigators. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. *N Engl J Med*. 2011;364:313–321. doi: 10.1056/NEJMoa1010663.

## Stop Randomizing All Cardiac Arrests Myron L. Weisfeldt

*Circulation*. 2016;134:2035-2036

doi: 10.1161/CIRCULATIONAHA.116.025302

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2016 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the  
World Wide Web at:

<http://circ.ahajournals.org/content/134/25/2035>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation* is online at:  
<http://circ.ahajournals.org/subscriptions/>