Toward Definitive Trials and Improved Outcomes of Cardiac Arrest

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The survival rate from out-of-hospital cardiac arrest has remained essentially unchanged in the United States for the past several decades, hovering in the 7% to 10% range overall. In communities with more frequent bystander performance of cardiopulmonary resuscitation (CPR), short emergency medical services response times, and hospital-based hypothermia, there is significantly better survival, particularly for patients whose cardiac arrests are witnessed and in those for whom ventricular tachycardia or ventricular fibrillation is the first recorded rhythm. Unfortunately, among the many randomized trials in resuscitation from cardiac arrest, few demonstrate improved survival to the point of hospital discharge. In-hospital hypothermia and use of an automated external defibrillator by a bystander are 2 of the few interventions shown to improve survival. Examples of prehospital interventions that failed to demonstrate improved survival to hospital discharge in clinical trials include antiarrhythmic and vasoactive drugs, as well as agents intended to provide cerebral protection or improved metabolism. In fact, a recent study reported no benefit from drugs versus no drugs used during the initial out-of-hospital resuscitative maneuvers.

Recent efforts to improve the outcomes of cardiac arrest have centered on inducing hypothermia in unconscious patients on admission to the hospital and providing better CPR through more consistent and continuous chest compression within a narrow range of compression rates, along with avoiding hyperventilation during resuscitation because it impedes blood flow. The focus of attention during resuscitation on optimizing blood flow through optimal chest compression is a reflection of both animal and human studies in which improved blood flow (via CPR) appears to result in improved survival. Such observations have led to a series of recent changes in the protocols for chest compressions and defibrillation attempts for out-of-hospital resuscitation. These recommended changes were embodied in the 2005 international CPR guidelines and were implemented without definitive testing over the past 5 years. Some of these changes are the focus of a study by Jost and associates in the Paris, France, emergency medical services system. The results are reported in this issue of Circulation.

The study was designed to test the value of some of the 2005 changes and appears to have been well conducted, with strict documentation of adherence to protocol. The investigators programmed automated external defibrillators to compare the pre-2005 guidelines (repeated shocks with only brief periods of chest compression between shocks, as well as pauses before and after each shock) with the post-2005 guidelines (single shock and continued CPR whenever possible). The post-2005 strategy includes no postshock pause in chest compression to feel for the pulse and 90 seconds of CPR between shocks. By reviewing the recordings of the ECG, chest impedance, and event notations from the automated external defibrillator, the investigators proved adherence to the protocol for the first 9 minutes of resuscitation by the providers. There was major separation between the 2 groups in relation to the 2 strategies tested in terms of shocks given, pause times before and after shock, and “hands on” percentage compression time and compression rate.

As reported, this study did not demonstrate improvement in return of spontaneous circulation in the field, increased admission to the hospital with a pulse, or better survival to hospital discharge or out to 1 year. Should we conclude that there is no evidence of clinical value for the new guidelines? Perhaps not. In this study, 1238 patients were randomized. Excluded from analysis were 3 appropriate groups of patients: Those who did not have a tachyarrhythmia but were shocked because of ECG artifacts, those with trauma, and those cases in which there were multiple arrest victims at the same time. This left 992 appropriately entered patients. However, data from 15% (n=147) of these patients were not included in the analyses because either the surviving patient or the family of a patient (who did not survive or was not able to give consent) refused participation in the study.

Because the primary outcomes of hospital admission with a pulse and return of spontaneous circulation in the field were nearly identical for the 2 groups, the authors conclude that “this improvement in CPR metrics did not translate into measurable differences in ROSC [return of spontaneous circulation] before ACLS [advanced cardiac life support] arrival.” However, if clinical utility of the new guidelines is considered, it is relevant to look at an arguably more important clinical outcome, such as survival to hospital discharge or beyond. In fact, there was a nonstatistically significant trend in survival to hospital discharge: 10.6% of control subjects survived to hospital discharge (pre-2005 guidelines), whereas 13.3% of intervention patients survived (post-2005 guidelines; P=0.19 with adjustments). This sug-
gests the possibility of a nearly 25% increase in survival to this point in time, which, if realized, would provide strong evidence to continue the change in practice.

Three issues cloud the interpretability of this result. First, the available sample size is inadequate to reliably detect an effect of such size. If the population percentages surviving to hospital discharge were the same as observed in the study by Jost et al, then sample sizes of more than 2300 per group would be needed to achieve a statistically significant effect with power of 0.80 (80% of the time).

Second, bias may result from the loss of nonconsented patients from the original cohort. The authors acknowledge that in omitting the 147 patients, “This may have biased all end points toward fewer surviving patients.” Although not explicitly stated in the article, this assumes that refusal of consent to use of data was higher for survivors than among patients who died. Although data are not presented to support such a claim, the authors conjecture that survivors or families learned of their randomization group and therefore refused to participate. Although the authors go on to add that the patients excluded owing to lack of consent were fairly evenly distributed between the 2 groups (ie, control pre-2005 and intervention post-2005), they indicate that “it is not known whether the portion of nonconsenting survivors is the same in both groups.” We can then consider the sensitivity of the result to the sorts of differential biases that might arise. For the sake of illustration, assume the extreme case in which all selection bias occurs in the intervention group; that is, survival rate does not vary by consent among those in the control group but is higher among nonconsented than consented patients in the intervention group. Then, a design that includes 147 nonconsented patients achieves power of 0.80 if the overall percentage survival to hospital discharge among interventional patients is 17.0% or higher, or in other words, in the intervention group, if patients for whom consent is not obtained are 2.9 times more likely to be survivors than those for whom consent is obtained. Under these conditions, the entire conclusion of the study may well have changed in favor of a positive effect on survival to hospital discharge if there had been an analysis of the entire eligible cohort. The change in guidelines would then be interpreted as one of the few interventions in the conduct of out-of-hospital cardiac resuscitation to improve outcomes. Of course, not all bias scenarios suggest such a possibility, and the realism of the line of reasoning just delineated depends on the plausibility both of the bias conjecture proposed by Jost et al and of any supposition that failure of consent is more strongly tilted to survivors in 1 treatment arm than in the other.

Third, loss of sample size resulting from patient omission erodes the precision with which survival percentages may be estimated. This constitutes a second mechanism that reduces the power to detect intervention effects.

The potential bias and loss of power related to nonconsent for use of data raise important challenges for resuscitation research. Despite the enormous public health burden related to cardiac arrest and the desire for evidence-based approaches to resuscitation, it is only ethically acceptable to conduct clinical research in the emergency setting when there is no possibility of obtaining a priori consent, under extremely limited conditions, and when a rigorous series of additional safeguards to ensure the welfare of participants are taken. These safeguards include heightened approval processes, community consultation, and the use of a data monitoring committee. To help ensure the safety of interventions tested under this exception, it is beneficial to have access to clinical information from the early post intervention period. Therefore, at least in the United States, information obtained before withdrawal from research is typically maintained in the study database. In the study by Jost et al, this would have included the analysis of information into the period of hospital admission, which would likely have provided data to help understand whether there was a bias related to survival at hospital discharge. Although it would be scientifically desirable to have additional clinical information for surviving patients, it would be clearly inappropriate to obtain it should the patient or their appropriate surrogate refuse consent for ongoing research activities.

Of course, the present study did not take place in the United States, and there are important differences in the laws and practices in different countries with respect to the permissibility of research conducted in the emergency setting and in privacy. Nevertheless, it is important to recognize that such differences may play an important role in whether particular trials are informative with respect to meaningful outcome measures. At minimum, it would seem desirable to attempt to collect data on the reason for refusal of consent so questions of potential bias could be addressed directly. Furthermore, given such differences and the ethical considerations that are at issue, it would also be desirable to explore the use of approaches that would not necessitate the use of data when patients and family members refuse. Modern statistics provide rigorous thinking and methodology on how to make causal inferences in the presence of this type of challenge. Although these cannot entirely eliminate biases that, after all, are unobservable, creative study designs that involve the collection of auxiliary data and their analysis by use of appropriate methods may lead to advances in reducing biases.

In addition to the issue of data availability, inclusion, and analysis, another major issue of concern relates to the fact that frustration has grown in the resuscitation research community about repeated negative trials involving single interventions. This frustration has led to “bundled” interventions, as exemplified by the present study. The assumption is that 1 intervention is not sufficient to show effectiveness, but a number of interventions in the same direction might. However, the fallacy of such an approach is that interventions chosen may be both good and bad, resulting in a null conclusion.

As related to the study by Jost et al, both a recent clinical study and animal research data have suggested that the resumption of chest compressions immediately after defibrillation will result in more frequent immediate recurrent fibrillation if the shock restores sinus rhythm. Recurrent fibrillation is a poor prognostic sign for survival. Would the return of spontaneous circulation and incidence of admission to the hospital with a pulse have been higher if only the changes in CPR performance, preshock interruptions, and no
stacked shocks had been studied, without the additional requirement of no postshock pause? This is unknown, but it underscores the potential difficulties in interpreting the findings from clinical research when interventions are bundled.

Conclusions
The profound public health burden associated with cardiac arrest makes evident the need for definitive clinical trials in resuscitation. Although the study by Jost et al13 demonstrates that it is possible to overcome considerable practical obstacles to conducting this research, there may be ways to enhance the likelihood of conducting definitive clinical research in the future. First, trials should be powered to be able to assess clinically meaningful outcome measures, such as survival to hospital discharge. Second, approaches should be developed and implemented to minimize the potential bias due to incomplete data. Third, caution should be exercised when designing trials in which interventions are bundled so that the results will be interpretable.

Disclosures
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References

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