More than 540,000 persons experience sudden cardiac arrest annually in the United States, the majority of which occur out-of-hospital.1 Neurologically favorable survival from out-of-hospital cardiac arrest (OHCA) has increased over the past decade,2-4 with the implementation of integrated systems of care focused on emergency response and systematic postresuscitation care.4-8 Despite these advances, mortality remains high after OHCA with only 5% to 15% survival to hospital discharge.1

Methods and Results—Retrospective cohort study of a cardiac arrest database at a single site. We included 1014 adult (≥18 years) patients experiencing nontraumatic out-of-hospital cardiac arrest between 2005 and 2011, defined as receiving cardiopulmonary resuscitation or defibrillation from a professional provider. We stratified by functional outcome at hospital discharge (modified Rankin scale). Survival to hospital discharge was 11%, but only 6% had a modified Rankin scale of 0 to 3. Within 16.1 minutes of cardiopulmonary resuscitation, 89.7% (95% confidence interval, 80.3%-95.8%) of patients with good functional outcome had achieved return of spontaneous circulation, and the probability of good functional recovery fell to 1%. Adjusting for prehospital and inpatient covariates, cardiopulmonary resuscitation duration (minutes) is independently associated with favorable functional status at hospital discharge (odds ratio, 0.84; 95% confidence interval, 0.72-0.98; P=0.02).

Conclusions—The probability of survival to hospital discharge with a modified Rankin scale of 0 to 3 declines rapidly with each minute of cardiopulmonary resuscitation. Novel strategies should be tested early after cardiac arrest rather than after the complete failure of traditional measures. (Circulation. 2013;128:2488-2494.)

Key Words: cardiopulmonary resuscitation ■ heart arrest ■ resuscitation

Clinical Perspective on p 2494

Besides immediate cardiopulmonary resuscitation (CPR), rapid defibrillation, and 1 to 2 mg of epinephrine, no other intervention has been demonstrated to increase the likelihood of return of spontaneous circulation (ROSC). Recently, even the long-term benefits of epinephrine have been questioned.9 When these interventions fail to achieve ROSC after a few minutes, some emergency medical services (EMS) systems transport patients in whom these interventions fail to the hospital, where the same resuscitation techniques are repeated. In either setting, no additional resources are brought to bear after the initial interventions fail, and the majority of patients who do not have rapid ROSC will not survive or experience a good functional outcome. Other EMS systems will terminate the resuscitation, based on the duration of resuscitation efforts, which has been included in some versions of the termination of resuscitation guidelines.10-12

Alternative approaches to treatment of OHCA, such as extracorporeal life support (ECLS), have yielded functionally favorable survival in selected patients in whom traditional CPR failed.13,15 However, the results of ECLS were poor when the initiation of the procedure was restricted to patients in whom 30 minutes or more of traditional resuscitation had failed.16 Choosing the optimal duration of traditional resuscitation after which to switch to an alternate approach requires an estimate of the probability of survival and functional recovery...
as a function of the duration of resuscitative efforts until ROSC. Longer durations of CPR during in-hospital cardiac arrest are associated with higher rates of ROSC and survival to discharge. However, similar data are lacking for OHCA. We analyzed data from EMS that do not use a rigid termination of resuscitation guideline. In this study, we describe the relationship between the duration of CPR until ROSC and functional outcome at hospital discharge to determine whether there is a duration of CPR after which repeating traditional resuscitation interventions ceases to result in meaningful survival.

Methods

Data Source
We examined cardiac arrest database data between December 2005 and April 2011 at the Pittsburgh site of the Resuscitation Outcomes Consortium. The Resuscitation Outcomes Consortium is a multicenter clinical trial network focused on cardiac arrest and severe traumatic injury that has previously been described in detail. Data for the cardiac arrest database are obtained under a waiver of informed consent, approved by the University of Pittsburgh institutional review board, and participating hospital institutional review boards, as well. In brief, research personnel at participating sites prospectively collect patient care reports, monitor ECG data, and review audio recordings from all consecutive patients having a cardiac arrest treated by participating EMS systems. Research coordinators review the hospital records for patients transported to the hospital to determine in-hospital interventions, in-hospital mortality, and functional status at the time of hospital discharge. Coordinators assigned a modified Rankin Scale (mRS) score at hospital discharge to each subject by review of all available chart information with the use of a standard chart-review instrument.

Study Design and Population
This was a retrospective cohort study of adult (age ≥18 years) patients experiencing OHCA. Cardiac arrest was defined as receiving chest compressions from a professional provider or rescue shocks from a professional provider or any automated external defibrillator. We excluded both suspected and confirmed cases of traumatic arrest.

Study Definitions and End Points
Our primary end point was survival to hospital discharge with favorable functional status, defined as mRS 0 to 3. Additionally, we classified patients into 3 other groups based on resuscitation outcome: survival to hospital discharge with unfavorable functional status (mRS 4–5), ROSC without survival to hospital discharge (mRS 6), and no ROSC. Resuscitation duration, defined as CPR duration in minutes, was the primary independent variable. CPR duration was defined as the time from first chest compression provided by EMS providers to the termination of resuscitation efforts either because of ROSC or declaration of death. Paramedics are permitted to cease resuscitative efforts at the scene after consultation with a physician either on the scene or via radio.

Time-stamped data (hours: minutes: seconds) on the initiation and conclusion of CPR by EMS providers were recorded by the monitor-defibrillator, which stays with the patient throughout resuscitation. CPR performance was detected either indirectly by changes in thoracic impedance recorded from external defibrillator electrodes or directly by an accelerometer between the rescuer and patient’s chest.

Statistical Analyses
Analyses were performed with STATA 12.0 (StataCorp, College Station, TX). We stratified patients by outcome and tabulated patient characteristics, cardiac arrest characteristics, EMS interventions, and inpatient interventions.

For the subset of patients achieving ROSC, we constructed simple curves of the proportion of subjects achieving ROSC over time, stratified by outcome (mRS 0–3, mRS 4–5, mRS 6), and compared distributions with the Kruskal-Wallis test. We then determined the estimated 50th, 75th, and 90th percentiles of CPR duration for each stratum. We also determined the duration of CPR corresponding to the estimated 50%, 75%, 90%, and 99% proportion of patients achieving ROSC, stratified by outcome. We used the data point closest to, but not exceeding, each proportion. Finally, we calculated the dynamic probability of survival with mRS 0 to 3 among all attempted resuscitations.

We created both unadjusted and adjusted logistic regression models to evaluate the association between CPR duration and mRS 0 to 3 on hospital discharge. We used 2 separate adjusted models to evaluate the association between CPR duration and survival to hospital discharge with mRS 0 to 3. Based on previous work, we adjusted each regression model for covariates that are associated with outcome. The first model was additionally adjusted for therapeutic hypothermia and cardiac catheterization, which are subsequent confounders that may have altered patient outcome.

Results
A total of n=5517 subjects experienced OHCA during the specified time frame, with 2349 treated by EMS and considered for analysis. Of these, 1042 had complete data for analysis of CPR duration. Subjects with complete CPR duration data did not differ in clinical features from the subjects excluded because of incomplete data. An additional 28 subjects were excluded because of missing survival or functional outcome data, leaving n=1014 for final analysis (Figure 1). Of these 1014 attempted resuscitations, 475 (47%) achieved ROSC, 113 (11%) survived to hospital discharge, and 58 (6%) had a favorable functional status.

Demographic and clinical features stratified by outcome are presented in Table 1. The simple curves and estimated percentiles of CPR duration for patients achieving ROSC, stratified by patient outcome, are presented in Figure 2. The distribution of CPR duration differed across strata (P=0.0001).

The dynamic probabilities and 95% confidence intervals for survival with mRS 0 to 3 among all resuscitations are presented in Figure 3. Each data point represents favorable...
The durations of CPR corresponding to estimated proportions of patients achieving ROSC are presented in Table 2. We selected data points closest to, but not exceeding, the 50%, 75%, and 90% function of ROSC. Within 9.3 minutes of CPR, 74.1% (95% confidence interval [CI], 62.5%–84.5%) of patients with good functional outcome had achieved ROSC. Within 16.1 minutes of CPR, 89.7% (95% CI, 80.3%–95.8%) of patients with good functional outcome had achieved ROSC.

The logistic regression models are presented in Table 3. Adjusting for prehospital covariates, CPR duration (minutes)
is independently associated with survival to hospital discharge with mRS 0 to 3 (odds ratio, 0.84; 95% CI, 0.75–0.95; \( P = 0.04 \)). Further adjusting for inpatient covariates, therapeutic hypothermia, and cardiac catheterization, CPR duration (minutes) is independently associated with survival to hospital discharge with mRS 0 to 3 (odds ratio, 0.84; 95% CI, 0.72–0.98; \( P = 0.02 \)).

### Discussion

In a single-site OHCA registry, we observed a rapidly diminishing probability of favorable functional status at hospital discharge with increasing durations of CPR (Figure 3). After 16.1 minutes of CPR, 89.7% (95% CI, 80.3%–95.8%) of patients with eventual mRS 0 to 3 at hospital discharge had achieved ROSC (Table 2). CPR duration was independently associated with favorable functional status, adjusting for both prehospital and inpatient covariates (Table 3).

Our findings suggest that conventional resuscitation strategies are most effective within the first 10 to 15 minutes, by which time >75% of patients with good functional recovery had already achieved ROSC (Figure 2). After 15 minutes, the probability of good functional recovery among all attempted resuscitations falls to \( \approx 2\% \) (Figure 3). Repeating the same therapies that did not work during the first 10 to 15 minutes does not result in incremental favorable survival.

Our findings highlight the need to implement novel resuscitation strategies in appropriate candidates who do not immediately respond to CPR, defibrillation, and the initial dose of epinephrine. An example intervention is ECLS for cardiac arrest resuscitation. This resource-intensive therapy has been successfully deployed to boost functionally favorable survival in selected candidates.\(^{13–15}\) However, the potential cost and resource intensity of ECLS mandate that it be applied in a rational manner with optimal chance to benefit the patient.

For interventions like ECLS to improve outcomes, it is critical that they not be implemented only after prolonged failure of traditional CPR. The traditional resuscitation paradigm emphasizes prompt attention to serial links in the chain of survival: early recognition of cardiac arrest and activation of the emergency response system, early CPR, early defibrillation, early advanced life support, and postresuscitation care. Our data demonstrate declining proportions of subjects who have favorable functional recovery with each minute that traditional CPR fails to achieve ROSC. Furthermore traditional resuscitation usually fails, making it reasonable to mobilize efforts to apply a novel therapy like ECLS immediately at the recognition of cardiac arrest, concurrently with traditional CPR. In those patients who achieve ROSC rapidly with traditional CPR, the mobilization of novel therapy can be discontinued.

Belohlavek et al\(^{26}\) propose a hyperinvasive approach to OHCA in the methods paper for the Prague OHCA Study. The authors propose a randomized parallel groups comparative study of mechanical chest compressions, prehospital intrarrest cooling, ECLS, and immediate coronary angiography in comparison with standard Advanced Cardiovascular Life Support–type care. Of note, subjects receive only 5 minutes of Advanced Cardiovascular Life Support, before randomization to the standard or hyperinvasive arm. The hyperinvasive approach hinges on rapid deployment of a mechanical chest compression device that facilitates immediate transport to a cardiac arrest center with CPR in progress. Patients who achieve ROSC during transport to the receiving center are still cooled and receive an invasive hemodynamic assessment consisting of coronary angiography, pulmonary angiography, aortography, and transthoracic echocardiography. ECLS is
patients with ROSC but persistent cardiogenic shock. Applied at the receiving center in patients without ROSC or CPR, cardiopulmonary resuscitation; mRS, modified Rankin scale; and ROSC, return of spontaneous circulation.

Earlier recognition of cardiac arrest coupled with earlier traditional therapies may still improve the proportion of

Table 2. CPR Durations That Correspond to the Estimated 50%, 75%, and 90% Proportions of Patients Achieving ROSC, Stratified by Outcome

<table>
<thead>
<tr>
<th>Patient Outcome</th>
<th>Proportion Achieving ROSC (95% CI)</th>
<th>CPR Duration, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0–3 (n=58)</td>
<td>50.0% (38.0%–63.4%)</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>74.1% (62.5%–84.5%)</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>89.7% (80.3%–95.8%)</td>
<td>16.1</td>
</tr>
<tr>
<td>mRS 4–5 (n=55)</td>
<td>49.1% (36.8%–62.9%)</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>74.6% (62.6%–85.1%)</td>
<td>18.1</td>
</tr>
<tr>
<td></td>
<td>87.3% (77.1%–94.5%)</td>
<td>23.4</td>
</tr>
<tr>
<td>mRS 6 (n=361)</td>
<td>49.9% (44.8%–55.1%)</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td>74.8% (70.2%–79.1%)</td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td>89.7% (86.4%–92.6%)</td>
<td>29.3</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CPR, cardiopulmonary resuscitation; mRS, modified Rankin scale; and ROSC, return of spontaneous circulation.

Table 3. Unadjusted and Adjusted Logistic Regression Models for mRS 0 to 3 on Hospital Discharge

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPR duration, min</td>
<td>0.87</td>
<td>0.83–0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prehospital adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPR duration, min</td>
<td>0.84</td>
<td>0.75–0.95</td>
<td>0.004</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.94</td>
<td>0.91–0.99</td>
<td>0.007</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.58</td>
<td>0.19–1.78</td>
<td>0.34</td>
</tr>
<tr>
<td>Witnessed arrest</td>
<td>4.91</td>
<td>1.29–18.67</td>
<td>0.02</td>
</tr>
<tr>
<td>AED shock delivered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence perfectly predicts failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>911 call to EMS arrival, min</td>
<td>1.00</td>
<td>0.85–1.18</td>
<td>0.99</td>
</tr>
<tr>
<td>Shockable initial rhythm</td>
<td>10.31</td>
<td>2.79–38.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest compression fraction, %</td>
<td>0.03</td>
<td>0.01–1.13</td>
<td>0.34</td>
</tr>
<tr>
<td>Advanced airway attempted</td>
<td>2.68</td>
<td>0.57–12.57</td>
<td>0.21</td>
</tr>
<tr>
<td>Epinephrine administered</td>
<td>0.46</td>
<td>0.11–1.91</td>
<td>0.29</td>
</tr>
<tr>
<td>Inpatient adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPR duration, min</td>
<td>0.84</td>
<td>0.72–0.98</td>
<td>0.02</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.93</td>
<td>0.89–0.97</td>
<td>0.002</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.71</td>
<td>0.20–2.54</td>
<td>0.61</td>
</tr>
<tr>
<td>Witnessed arrest</td>
<td>4.38</td>
<td>1.07–18.03</td>
<td>0.04</td>
</tr>
<tr>
<td>AED shock delivered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence perfectly predicts failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>911 call to EMS arrival, min</td>
<td>0.97</td>
<td>0.82–1.16</td>
<td>0.76</td>
</tr>
<tr>
<td>Shockable initial rhythm</td>
<td>3.35</td>
<td>0.78–14.34</td>
<td>0.10</td>
</tr>
<tr>
<td>Chest compression fraction, %</td>
<td>0.06</td>
<td>0.01–2.84</td>
<td>0.15</td>
</tr>
<tr>
<td>Advanced airway attempted</td>
<td>1.17</td>
<td>0.25–5.43</td>
<td>0.84</td>
</tr>
<tr>
<td>Epinephrine administered</td>
<td>0.37</td>
<td>0.08–1.71</td>
<td>0.20</td>
</tr>
<tr>
<td>Therapeutic hypothermia</td>
<td>0.40</td>
<td>0.12–1.35</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>5.85</td>
<td>1.58–21.64</td>
<td>0.008</td>
</tr>
</tbody>
</table>

AED indicates automate external defibrillator; CI, confidence interval; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and mRS, modified Rankin scale.

survivors with good functional outcome at hospital discharge. However, current resuscitation strategies have been optimized for the past 58 years, since the inception of manual external chest compressions.27 Observational studies and clinical trials with subsequent guideline updates have refined CPR quality,29–31 defibrillation timing,15 and pharmacological intervention,32–34 but the essence of cardiac arrest resuscitation has not fundamentally changed. A new paradigm may be needed to achieve more than modest improvements in patient outcome.

We advise caution about using these data to guide the incorporation of CPR duration into termination of resuscitation guidelines. Our data are derived from a subset of the population at a single site. Subjects were hospitalized at a variety of hospitals with varying sophistication of postcardiac arrest care. Anecdotally, during this same time period, the authors treated OHCA patients from other EMS systems who displayed good functional recovery despite total CPR durations of >21 minutes. These anecdotal cases may be explained by the 95% CIs for the estimations of CPR duration (Figure 2), probabilities of achieving ROSC (Table 2), and probabilities of mRS 0 to 3 on hospital discharge (Figure 3). Larger data sets may provide more precise estimates of the longest tolerable CPR duration. Finally, our primary outcome, functional status at hospital discharge, is a surrogate for long-term recovery. We have previously demonstrated that a large proportion of patients leaving the hospital have significant functional deficits,35 but that patients continue to improve after hospital discharge.36

Limitations

These are retrospective data are from a single-center registry. As such, there may be unmeasured biases in EMS treatment and local culture that influence resuscitation effort duration. One agency in our system dispatches a physician to each OHCA and termination of resuscitation at the scene is common. Additionally, the postresuscitative care and prognostic workup may differ between hospitals that care for these patients. A larger cohort is necessary to determine the generalizability of our results. Furthermore, we are subject to an inherent limitation of outcome-driven cardiac arrest research: patients without ROSC do not achieve subsequent outcomes. In this manner, outcomes after cardiac arrest are typically skewed with respect to CPR duration. However, we also note that outcome after ROSC appears to be a function of CPR duration. Patients that achieve ROSC after brief CPR durations are more likely to have improved functional outcome. Likewise, patients that achieve ROSC after longer CPR durations are more likely to have poor functional outcome.

Conclusions

Most CPR efforts fail to produce sustained ROSC after OHCA. Despite some increase in the total number of patients with ROSC when CPR is prolonged, the proportion of OHCA cases that survive to hospital discharge with favorable functional status declines with each minute of CPR. Alternative strategies to traditional resuscitation should be tested immediately after cardiac arrest rather than after the failure of traditional CPR.
Acknowledgments
We thank Joe Condle for his invaluable assistance maintaining the Pittsburgh ROC epistry. The ROC Data Coordinating Center did not partake in the analyses or conclusions. We also acknowledge the assistance of Joyce (Chung-Chou) H. Chang, PhD, Professor Medicine, Biostatistics, and Clinical and Translational Science at the University of Pittsburgh, with statistical methodology.

Sources of Funding
The Pittsburgh ROC site is supported by grant HL077871 from the National Heart, Lung, and Blood Institute, National Institutes of Health.

Disclosures
None.

References
Despite advances in systematic postresuscitation care, only 5% to 15% of out-of-hospital cardiac arrest victims survive to hospital discharge. Few interventions have proven benefit in cardiac arrest resuscitation, and the typical strategy for patients without rapid return of spontaneous circulation is to repeat failed interventions. No additional resources are brought to bear. Novel approaches to treating out-of-hospital cardiac arrest, such as extracorporeal life support, have yielded neurologically favorable survival in select patients in whom traditional resuscitation fails. We investigated the relationship between the duration of cardiopulmonary resuscitation and neurological outcome after cardiac arrest to identify the duration of cardiopulmonary resuscitation beyond which repeating traditional resuscitation measures does not result in incremental neurologically favorable survival. Our findings suggest that conventional resuscitation is the most effective within the first 10 to 15 minutes, by which time 75% of patients with favorable neurological recovery had achieved rapid return of spontaneous circulation. The probability of favorable neurological recovery fell to 2% beyond this point. Cardiopulmonary resuscitation duration was independently associated with favorable neurological outcome, adjusting for prehospital and inpatient covariates. Alternative strategies to traditional resuscitation should be tested immediately after cardiac arrest, rather than after the failure of traditional cardiopulmonary resuscitation.

Go to http://cme.ahajournals.org to take the CME quiz for this article.
Duration of Resuscitation Efforts and Functional Outcome After Out-of-Hospital Cardiac Arrest: When Should We Change to Novel Therapies?
Joshua C. Reynolds, Adam Frisch, Jon C. Rittenberger and Clifton W. Callaway

_Circulation_. 2013;128:2488-2494; originally published online November 17, 2013; doi: 10.1161/CIRCULATIONAHA.113.002408

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 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/128/23/2488

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/