Association Between Duration of Resuscitation and Favorable Outcome After Out-of-Hospital Cardiac Arrest

Implications for Prolonging or Terminating Resuscitation

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BACKGROUND: Little evidence guides the appropriate duration of resuscitation in out-of-hospital cardiac arrest, and case features justifying longer or shorter durations are ill defined. We estimated the impact of resuscitation duration on the probability of favorable functional outcome in out-of-hospital cardiac arrest using a large, multicenter cohort.

METHODS: This was a secondary analysis of a North American, single-blind, multicenter, cluster-randomized, clinical trial (ROC-PRIMED [Resuscitation Outcomes Consortium Prehospital Resuscitation Using an Impedance Valve and Early Versus Delayed]) of consecutive adults with nontraumatic, emergency medical services–treated out-of-hospital cardiac arrest. Primary exposure was duration of resuscitation in minutes (onset of professional resuscitation to return of spontaneous circulation [ROSC] or termination of resuscitation). Primary outcome was survival to hospital discharge with favorable outcome (modified Rankin scale [mRS] score of 0–3). Subjects were additionally classified as survival with unfavorable outcome (mRS score of 4–5), ROSC without survival (mRS score of 6), or without ROSC. Subject accrual was plotted as a function of resuscitation duration, and the dynamic probability of favorable outcome at discharge was estimated for the whole cohort and subgroups. Adjusted logistic regression models tested the association between resuscitation duration and survival with favorable outcome.

RESULTS: The primary cohort included 11 368 subjects (median age, 69 years [interquartile range, 56–81 years]; 7121 men [62.6%]). Of these, 4023 (35.4%) achieved ROSC, 1232 (10.8%) survived to hospital discharge, and 905 (8.0%) had an mRS score of 0 to 3 at discharge. Distribution of cardiopulmonary resuscitation duration differed by outcome ($P<0.00001$). For cardiopulmonary resuscitation duration up to 37.0 minutes (95% confidence interval, 34.9–40.9 minutes), 99% with an eventual mRS score of 0 to 3 at discharge achieved ROSC. The dynamic probability of an mRS score of 0 to 3 at discharge declined over elapsed resuscitation duration, but subjects with initial shockable cardiac rhythm, witnessed cardiac arrest, and bystander cardiopulmonary resuscitation were more likely to survive with favorable outcome after prolonged efforts (30–40 minutes). After adjustment for prehospital (odds ratio, 0.93; 95% confidence interval, 0.92–0.95) and inpatient (odds ratio, 0.97; 95% confidence interval, 0.95–0.99) covariates, resuscitation duration was associated with survival to discharge with an mRS score of 0 to 3.

CONCLUSIONS: Shorter resuscitation duration was associated with likelihood of favorable outcome at hospital discharge. Subjects with favorable case features were more likely to survive prolonged resuscitation up to 47 minutes.

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Clinical Perspective

What Is New?

- In this multicenter North American study of >11 000 patients with out-of-hospital cardiac arrest, we describe the relationship between duration of cardiopulmonary resuscitation and the likelihood of survival with favorable neurological outcome.
- There is a steady and predictable decline in the likelihood of survival with favorable neurological outcome as the duration of cardiopulmonary resuscitation accumulates. This decline is qualitatively different for subjects with different features of out-of-hospital cardiac arrest (shockable initial cardiac rhythm, witnessed cardiac arrest, bystander cardiopulmonary resuscitation).
- The duration of cardiopulmonary resuscitation independently predicts survival with favorable neurological outcome after adjustment for other factors.

What Are the Clinical Implications?

- Conventional resuscitation is most effective within the first 20 minutes, by which time 90% of patients with favorable neurological recovery had achieved return of spontaneous circulation.
- Patients with shockable initial cardiac rhythms, witnessed cardiac arrest, and bystander cardiopulmonary resuscitation were more likely to survive with favorable neurological outcome after resuscitation efforts >20 minutes.
- Hypothetical termination of resuscitation based solely on duration of cardiopulmonary resuscitation would have resulted in unacceptable losses of subjects with ultimate favorable neurological outcome.

More than 356 000 people experience sudden out-of-hospital cardiac arrest (OHCA) annually in the United States,[1–3] and little evidence guides the appropriate duration of resuscitation in OHCA. When initial prehospital resuscitation measures fail to achieve return of spontaneous circulation (ROSC), some emergency medical services (EMS) systems transport patients with ongoing cardiopulmonary resuscitation (CPR) to hospital, where the same therapies are typically repeated. In either setting, few additional resources are brought to bear, and most patients without rapid ROSC will not survive or experience good functional outcome.[4] Other EMS systems terminate the resuscitation on the basis of case features, termination of resuscitation (TOR) guidelines, or practical consideration of resuscitation duration. The ideal incorporation of resuscitation duration into decisions to continue or terminate resuscitation is unclear. Some guidelines advocate ≥20 minutes of resuscitation,[5–7] whereas others require structured assessment after 3 cycles of CPR and rhythm analysis (6 minutes)[8] or merely brief attempts (1–2 minutes) in subjects with unfavorable case features.[9] Still others do not incorporate resuscitation duration,[10] leaving clinicians to make ad hoc decisions at their discretion.

Multicenter, observational data on in-hospital cardiac arrest suggest that patients treated at hospitals with systematically longer durations of resuscitation attempts have a higher likelihood of ROSC and survival to discharge.[11] Other than 1 observational study of Japanese bystander-witnessed OHCA,[12] similarly robust patient-level data are limited for OHCA. In a single-site registry, we previously identified that after 20 minutes of traditional interventions, repeating these interventions yielded minimal incremental survival with favorable neurological outcome.[4]

Our objective was to estimate the impact of resuscitation duration (until ROSC or TOR) on the probability of favorable functional outcome in OHCA using a large, multicenter cohort. We analyzed clinical trial data to plot accrual of subjects with favorable and unfavorable outcomes over time, to estimate dynamic probabilities of favorable functional outcome as a function of resuscitation duration, and to test the association between resuscitation duration and favorable functional outcome. We also performed subgroup analyses to determine whether subjects with particular phenotypes or case features justified prolonging or terminating resuscitation.

METHODS

Data Source

We examined deidentified clinical trial data from the ROC (Resuscitation Outcomes Consortium) PRIMED trial (Prehospital Resuscitation Using an Impedance Valve and Early Versus Delayed),[13,14] which was conducted with exception from informed consent under US and Canadian regulations. Institutional Review boards at participating sites provided approval. Trial data were obtained from the National Institutes of Health Biological Specimen and Data Repository Information Coordinating Center. The Michigan State University Institutional Review Board granted waiver of consent for this secondary analysis of a deidentified data set. The original trials were neutral for differences between interventions,[13,14] avoiding confounding from trial arms.

ROC comprises 10 regional centers across North America and their respective EMS systems. The geographic footprint of ROC spans 218 prehospital agencies covering 35 000 sq miles and 24 million people. From June 2007 to July 2010, 150 EMS agencies participated in PRIMED. A detailed description of methodology has been given previously.[15,16] PRIMED studied 2 different resuscitation strategies: 30 versus 3 minutes of CPR before initial rhythm analysis and an impedance valve versus sham device during OHCA.[13,14] Research personnel at participating sites prospectively collected patient-level data, including prehospital data streams and audio recordings, from consecutive OHCA subjects. They reviewed hospital records to determine in-hospital interventions, in-hospital mortality, and functional status at hospital discharge. A modified Rankin Scale (mRS) score was assigned at hospital discharge

with a standardized chart review instrument. All participating ROC sites provided data for this study.

Study Design and Population

This was a retrospective cohort study of EMS-treated adult subjects experiencing OHCA. Cardiac arrest was defined as receiving chest compressions or rescue shocks from a professional provider or automated external defibrillator. We excluded suspected and confirmed cases of traumatic arrest.

Study Definitions and Outcomes

The primary outcome was survival to hospital discharge with favorable functional status (mRS score of 0–3). We classified subjects into 3 other groups based on resuscitation outcome: survival to hospital discharge with unfavorable functional status (mRS score of 4–5), ROSC without survival to hospital discharge (mRS score of 6), and no ROSC. Resuscitation duration (CPR duration in minutes) was the primary independent variable. CPR duration was defined as elapsed time from first professional chest compression to first ROSC or TOR. TOR guidelines were according to local protocol without input from the primary investigation or ROC. Some sites use rigid guidelines,[6] whereas others allow paramedics to terminate resuscitation at the scene after consultation with a physician. Among ROC sites, transport is typically initiated in the absence of documented ROSC for 58% of cases (site range, 14%–95%).[17]

Time-stamped data (hours:minutes:seconds) on initiation and conclusion of CPR by EMS providers were recorded by the monitor-defibrillator, which stayed with the patient throughout resuscitation. CPR was detected indirectly by changes in thoracic impedance recorded from external defibrillator electrodes or directly by an accelerometer between the rescuer and patient's chest. CPR quality for the initial 10 minutes of resuscitation was assessed by chest compression fraction, the proportion of time in which chest compressions were performed during each minute of resuscitation.

Statistical Analyses

Analyses were performed with STATA 12.0 (StataCorp, College Station, TX). We stratified subjects by outcome and tabulated subject characteristics, cardiac arrest characteristics, EMS interventions, and inpatient interventions. We compared these variables across outcomes with 1-way ANOVA (Kruskal-Wallis test for nonparametric variables) and the χ^2 or Fisher exact test. In this deidentified data set, age >89 years was not specified. To preserve age as a continuous variable, we coded any age >89 years as 90 years.

We constructed simple curves of the proportion of subjects achieving ROSC over time stratified by outcome (mRS score of 0–3, mRS score of 4–5, mRS score of 6, no ROSC) and compared distributions with the log-rank test. We then estimated the 50th, 75th, and 99th percentiles of CPR duration for each stratum.

We also calculated the dynamic probability of survival to hospital discharge with an mRS score of 0 to 3 among all attempted resuscitations and predefined subgroups to determine whether subjects with particular case features associated with favorable outcome (witnessed arrest, shockable initial rhythm, bystander CPR, and quartiles of EMS dispatch interval [9-1-1 call to onset of professional resuscitation]) have incremental benefit in prolonging resuscitation. We plotted the dynamic probabilities of an mRS score of 0 to 3 for representative subject phenotypes with different combinations of these case features.

Last, we created unadjusted and adjusted logistic regression models to test the association between CPR duration and an mRS score of 0 to 3 at hospital discharge. Because factors that affect short-term survival may have blunted or opposite relationships with later survival,[18] we used 2 separate models to test the association between CPR duration and survival to hospital discharge with an mRS score of 0 to 3: a prehospital model and an inpatient model. The prehospital model including all subjects was adjusted for a priori prehospital covariates associated with outcome (age, sex, witnessed arrest, bystander CPR, EMS dispatch interval, shockable initial rhythm, mean chest compression fraction, advanced airway attempts [endotracheal intubation or supraglottic airway], and epinephrine administration).[13,14] The inpatient model including only subjects who survived to hospital admission was further adjusted for a priori inpatient interventions associated with outcome (induced hypothermia[19,20] and cardiac catheterization[21,22]). We tested model discrimination with the c statistic and model fit with Hosmer-Lemeshow goodness-of-fit test. Unfortunately, the deidentified nature of this data set precluded determination of the site at which subjects were enrolled, rendering adjustment for regional variability or clustering impossible.

RESULTS

Among a 24 million total catchment population, the PRIMED data set captured 17 445 subjects. Of these, 11 368 had complete time and outcome data (Figure 1). Among 11 368 attempted resuscitations, 4023 (35.4%) subjects achieved ROSC, 1232 (10.8%) survived to hospital discharge, and 905 (8.0%) had an mRS score of 0 to 3 at hospital discharge. Median professional CPR duration was 20 minutes (IQR, 12–27.3 minutes) overall, 13.5 minutes (IQR, 8–20 minutes) for those with ROSC, and 23.4 minutes (IQR, 16.5–30 minutes) for those without ROSC. The longest observed duration of CPR was

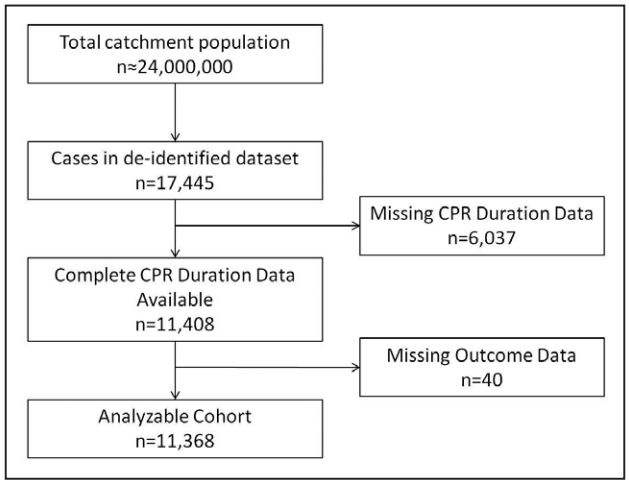

Figure 1. Study cohort and exclusions.
CPR indicates cardiopulmonary resuscitation.

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202 minutes in any subject and 47 minutes in subjects with eventual an mRS score of 0 to 3.

Table 1 contains demographic and clinical features stratified by outcome. CPR duration, prevalence of case features, EMS interventions, and inpatient interventions differed by outcome. Figure 2 shows curves and estimated percentiles of CPR duration for subjects achieving ROSC stratified by patient outcome. The distribution of CPR duration differed across strata ($P<0.00001$).

Figures 3 and 4 present dynamic probabilities and 95% confidence intervals (CIs) of survival with mRS scores of 0 to 3 for case features and patient phenotypes. Each point on the curve represents favorable functional outcome among subjects with CPR durations greater than or equal to the respective interval. We did not observe systematic bias for or against prolonged resuscitation among patient phenotypes. Although median CPR duration differed by case features (Table I in the online-only Data Supplement), the likelihood of still receiving CPR at a given elapsed interval was consistent across phenotypes (50% of subjects were still receiving CPR at 20 minutes, 20% at 30 minutes, and 5% at 40 minutes; Figure 4). Stratification by initial cardiac rhythm had the greatest discrepancy in probability of an mRS score of 0 to 3, followed by witnessed cardiac arrest, bystander CPR, and EMS dispatch interval (Figure 3). Subjects with shockable initial cardiac rhythm, witnessed arrest, and bystander CPR had the highest probability of an mRS score of 0 to 3 at hospital discharge, 2-fold to 3-fold higher than other phenotypes (Figure 4).

Table 2 contains logistic regression models. In unadjusted analysis, CPR duration (minutes) was associated with survival to hospital discharge with an mRS score of 0 to 3 (odds ratio [OR], 0.87; 95% CI, 0.86–0.87; $P<0.0001$). After adjustment for prehospital covariates, CPR duration was independently associated with survival to hospital discharge with an mRS score of 0 to 3 (OR, 0.93; 95% CI, 0.92–0.95; $P<0.0001$; c statistic, 0.93). After further adjustment for inpatient covariates among subjects surviving to hospital admission, the independent association persisted (OR, 0.97; 95% CI, 0.95–0.99; $P=0.04$; c statistic, 0.91). Final adjusted models had acceptable fit ($P=0.97$ and $P=0.98$). Given 33% missing data for mean chest compression fraction, we performed post hoc sensitivity analyses with multiple imputations for mean chest compression fraction in the logistic regression models. Neither the magnitude or significance of the ORs for both the predictor variable of interest (CPR duration) and the imputed variable (mean chest compression fraction) differed between models with complete cases and imputed data.

DISCUSSION

In a multicenter cohort of >11 000 subjects, we observed rapidly diminishing probability of favorable functional status at hospital discharge with increasing durations of CPR. After 37.0 minutes of CPR (95% CI, 34.9–40.9 minutes), 99% of subjects with an eventual mRS score of 0 to 3 at hospital discharge had achieved ROSC (Figure 2). Moreover, we calculated dynamic, time-based probability estimates of favorable outcome for specific key patient features (Figures 3 and 4). CPR duration was independently associated with favorable functional status after adjustment for both prehospital and inpatient covariates (Table 2).

The appropriate duration of resuscitation in cardiac arrest is fraught with clinical and ethical implications. Our findings suggest that with conventional resuscitation, 90% of subjects with good outcome have ROSC within 20 minutes and 99% within 37 minutes (Figure 2). Our data can address 3 clinical questions: In which phenotypes/subgroups are prolonged resuscitation efforts justified? In which subgroups may shorter attempts before TOR be appropriate? When should novel resuscitation strategies be initiated in appropriate candidates?

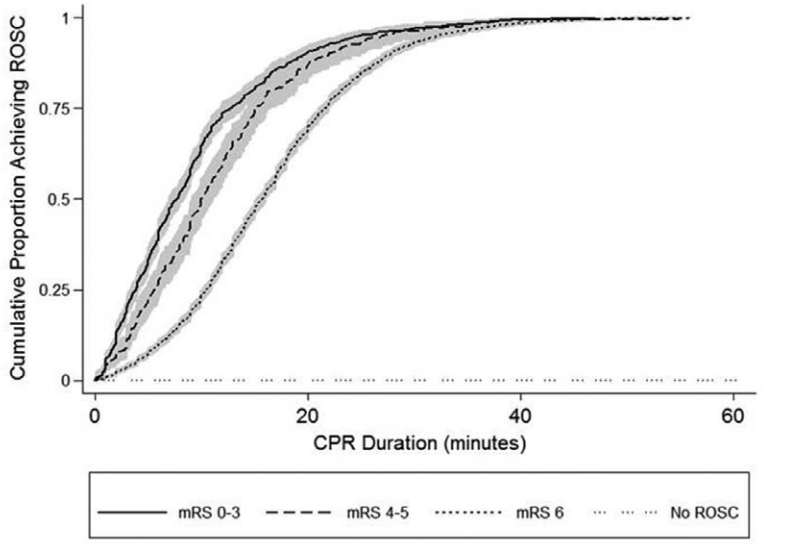
Prolonged resuscitation efforts appear worthwhile in subjects with shockable initial cardiac rhythm, witnessed cardiac arrest, bystander CPR, or a brief interval between collapse and professional resuscitation (Figure 3). Shockable initial rhythm appears to be the best prognostic indicator (Figures 3A and 4A). Among those with shockable initial cardiac rhythms, witnessed cardiac arrest appears to be a better prognostic indicator than bystander CPR (Figure 4A). This may reflect a greater ischemic insult in unwitnessed cardiac arrest that is not reversible even with earlier reperfusion provided by bystander CPR. The longest duration of professional CPR observed in any subject with an eventual mRS score of 0 to 3 was 47 minutes. We observed no additional accrual of subjects with an eventual mRS score of 0 to 3 beyond 47 minutes among those with shockable initial cardiac rhythm, 41 minutes among those with witnessed cardiac arrest, and 47 minutes among those with bystander CPR. Because resuscitation efforts longer than this were so rare, these data cannot determine futility to continue efforts longer. Likewise, the median duration of CPR was 23.4 minutes in subjects without ROSC. It is unknown how those subjects would have fared had resuscitation continued longer. These findings are consistent with findings by Grunau et al[23] and Nehme et al,[24] who studied the impact of shockable initial cardiac rhythm and EMS-witnessed cardiac arrest on resuscitation duration and survival in a single EMS system. They found higher "resilience" to resuscitation lasting 30 to 40 minutes in subjects with shockable initial cardiac rhythms and EMS-witnessed cardiac arrest. Nonetheless, we expect that beyond some ultimate duration of resuscitation, incremental survival becomes asymptotic.

Goldberger et al[11] compared median duration of resuscitation attempts in nonsurvivors of in-hospital cardiac arrest to assess the tendency of hospitals for

Table 1. Clinical Features Stratified by Functional Outcome at Hospital Discharge

	Missing Data (n=11 368), n (%)	mRS Score			ROSC=0 (n=7,345)	*P* Value
		0–3 (n=905)	4–5 (n=327)	6 (n=2791)		
Baseline characteristics						
Age (IQR), y	38 (0.3)	59 (49–68)	66 (57–76)	72 (59–82)	70 (56–82)	0.0001
Male sex, (%)	1 (0.01)	666 (73.6)	205 (62.7)	1650 (59.1)	4600 (62.6)	<0.001
Residence before event, %						<0.001
Home		880 (97.2)	276 (84.4)	1616 (60.0)	220 (3.0)	
Rehabilitation center		1 (0.1)	4 (1.2)	72 (0.3)	4 (0.1)	
Assisted living facility		6 (0.7)	9 (2.8)	53 (1.9)	11 (0.2)	
Nursing home		3 (0.3)	31 (9.5)	165 (5.9)	7 (0.1)	
Unknown		15 (1.7)	7 (2.1)	890 (31.9)	7110 (96.8)	
Event characteristics, n (%)						
Witnessed status	0 (0)	739 (81.7)	254 (77.7)	1718 (61.6)	2606 (35.5)	<0.001
EMS-witnessed	0 (0)	189 (20.9)	52 (15.9)	353 (12.6)	408 (5.6)	<0.001
Bystander-witnessed	1260 (11)	550 (60.8)	202 (61.8)	1365 (48.9)	2198 (29.9)	<0.001
Bystander CPR	0 (0)	415 (45.9)	138 (42.2)	1102 (39.5)	2673 (36.4)	<0.001
AED shock delivered	11 196 (98)	25 (2.8)	6 (1.8)	29 (1.0)	28 (0.4)	<0.001
Initial ECG rhythm						<0.001
VF/VT		673 (74.4)	166 (50.8)	706 (25.3)	977 (13.3)	
PEA		129 (14.3)	97 (29.6)	928 (33.3)	1421 (19.4)	
Asystole		45 (5.0)	45 (13.8)	900 (32.3)	4190 (57.1)	
AED, no shock advised		34 (3.8)	11 (3.4)	232 (8.3)	690 (9.4)	
Unknown		11 (1.2)	3 (0.9)	18 (0.6)	64 (0.9)	
EMS interventions						
Time from 9-1-1 call to EMS arrival (IQR), min	0 (0)	7.8 (6.1–10.5)	8.1 (6.0–10.7)	8.5 (6.7–11.1)	8.5 (6.8–10.7)	0.0001
CPR duration, min	0 (0)	7.7 (3.9–12.7)	10.0 (5.7–15.3)	15.7 (10.5–21.7)	23.4 (16.5–30.0)	0.0001
Mean CCF first 10 min	3843 (33)	0.66±0.19	0.67±0.18	0.72±0.15	0.72±0.14	<0.001
Advanced airway attempted, n (%)	0 (0)	680 (75.1)	280 (85.6)	2633 (94.3)	6120 (83.3)	<0.001
Endotracheal intubation, n (%)	0 (0)	639 (70.6)	263 (80.4)	2455 (88.0)	5518 (75.1)	<0.001
Supraglottic airway, n (%)	0 (0)	60 (6.6)	27 (8.3)	272 (9.8)	922 (12.6)	<0.001
Epinephrine administered, n (%)	33 (0.3)	376 (41.6)	211 (64.5)	2451 (87.8)	6160 (83.9)	<0.001
Dose of epinephrine, mg	2180 (19)	2.2±1.7	2.4±1.7	2.8±1.8	3.8±1.9	<0.001
Any shock delivered, n (%)	4 (0.04)	711 (78.6)	194 (59.3)	1113 (39.9)	2081 (28.3)	<0.001
Shocks delivered (IQR), n	7273 (64)	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)	0.33
Inpatient interventions						
Therapeutic hypothermia, n (%)	0 (0)	453 (50.0)	177 (54.1)	856 (30.7)	NA	<0.001
Cardiac catheterization, n (%)	1783 (16)	457 (50.5)	84 (25.7)	184 (6.6)		<0.001
PCI, n (%)	1783 (16)	334 (36.9)	59 (18.0)	152 (5.5)		<0.001
CABG, n (%)	1783 (16)	67 (7.4)	11 (3.4)	6 (0.2)		<0.001
Pacemaker/ICD implantation, n (%)	0 (0)	308 (34.0)	37 (11.3)	21 (0.8)		<0.001
ICU length of stay (IQR), d	859 (8)	6 (4–11)	10 (6–18)	3 (1–5)		0.0001
DNR order, n (%)	836 (7)	26 (2.9)	99 (30.3)	1,732 (62.1)		<0.001

Continuous variables are given as mean±SD or median (interquartile range [IQR]). Categorical variables are given as count (%). AED indicates automated external defibrillator; CABG, coronary artery bypass graft; CCF, chest compression fraction; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate; EMS, emergency medical services; ICD, implantable cardiac defibrillator; ICU, intensive care unit; mRS, modified Rankin Scale; PCI, percutaneous coronary intervention; PEA, pulseless electric activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.



	Percentile CPR duration (minutes) 95% confidence interval			
	50th Percentile	75th Percentile	90th Percentile	99th Percentile
mRS 0-3 (n=905)	7.7 (7.0, 8.3) min	12.7 (11.8, 14.0) min	19.8 (18.4, 21.3) min	37.0 (34.9, 40.9) min
mRS 4-5 (n=327)	10.0 (9.2, 11.0) min	15.3 (14.4, 16.5) min	22.0 (20.0, 25.0) min	37.5 (34.6, --) min
mRS 6 (n=2,791)	15.7 (15.2, 16.0) min	21.7 (21.1, 22.0) min	28.0 (27.1, 28.5) min	42.0 (40.5, 45.0) min
No ROSC (n=7,345)	--	--	--	--

Figure 2. Distribution of cardiopulmonary resuscitation (CPR) duration for all patients with attempted resuscitation stratified by outcome (P<0.00001).
Point estimates and 95% confidence intervals for percentiles of CPR duration are provided in the accompanying table. The upper bound of the 95% confidence interval for the 99th percentile of CPR duration could not be estimated for modified Rankin Scale (mRS) scores of 4 to 5 because it exceeded the values of this data set. ROSC indicates return of spontaneous circulation.

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duration of resuscitation efforts and related this tendency to survival. Subjects at hospitals with longer resuscitation attempts were more likely to achieve ROSC and to survive to hospital discharge. It is important to note that there was no difference in proportion of good functional outcome at hospital discharge between groups. This was compelling evidence that prolonging resuscitation efforts can increase survival without a substantial increase in severe neurology injury among survivors. Our data identify patient phenotypes in OHCA most likely to benefit from this approach.

Conversely, clinicians may use resuscitation duration in the absence of ROSC to justify TOR after some elapsed interval. At face value, the probability curves in Figure 3 appear to support this in subjects with unfavorable case features. One commonly accepted definition of medical futility is <1% probability of success.[25,26] The upper bound of the 95% CI fell below 1% after 12 minutes of CPR in the subgroup with nonshockable initial cardiac rhythm and after 17 minutes of CPR in the subgroup with unwitnessed cardiac arrest. However, hypothetical termination at these points would have missed 53 (23%) and 26 (16%) subsequent subjects with favorable outcome, respectively. Drennan et al[27] tested the combination of CPR duration and absence of ROSC as a hypothetical TOR rule. In their cohort, hypothetical TOR based solely on absence of ROSC after 20 minutes of resuscitation would have missed 10% of all survivors and 10% of survivors with favorable functional outcome. Taken together, these data argue against using resuscitation duration in isolation or with ad hoc case features to justify TOR. Instead, we turn attention to validated TOR decision rules.[28,29]

Last, our findings support consideration of novel resuscitation strategies in appropriate candidates who do not immediately respond to conventional resuscitation. The current strategies have been optimized for 60 years, but the essence of resuscitation has not fundamentally changed. A new paradigm may be needed to achieve more than modest improvements in patient outcome. One such intervention is extracorporeal CPR (E-CPR), the incorporation of extracorporeal life support into cardiac arrest resuscitation.[30] This resource-intensive therapy is associated with improved functionally favorable survival in selected candidates with favorable case features.[31–33] However, the cost and resource intensity of E-CPR mandate that it be applied in a rational manner with optimal chance to benefit patients. Our data demonstrate declining proportions of subjects who have favorable recovery with each minute that traditional CPR fails to achieve ROSC. Furthermore, traditional resuscitation usually fails, making it reasonable to mobilize a novel therapy such as E-CPR early after recognition of cardiac arrest with a favorable phenotype that can withstand prolonged efforts concurrently with traditional CPR. Considering the time demands of transporting to hospital and initiating E-CPR, early mobilization is also logistically

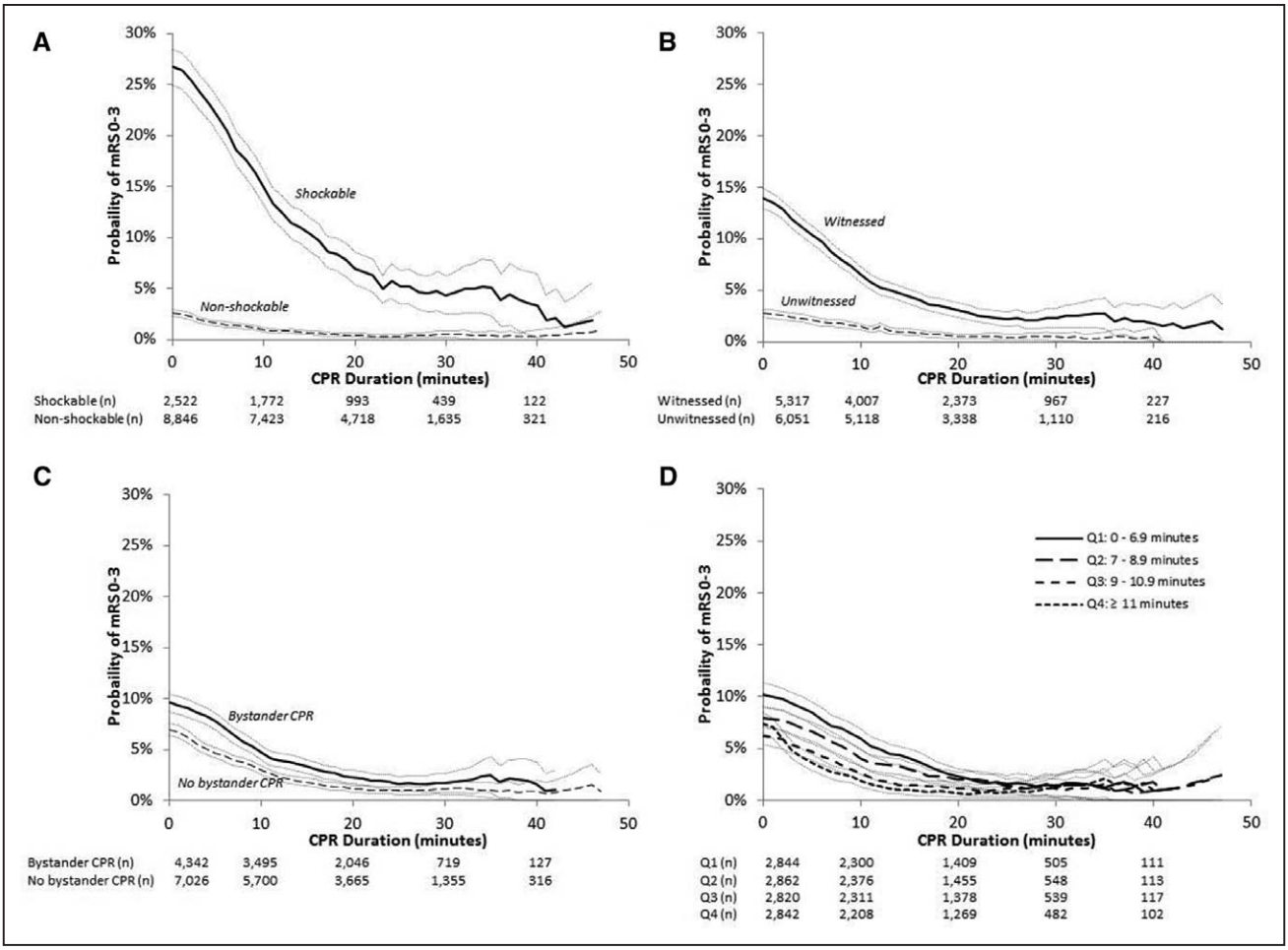

Figure 3. Dynamic probability (black lines) with 95% confidence intervals (gray lines) of survival to hospital discharge with modified Rankin Scale (mRS) score of 0 to 3 as a function of cardiopulmonary resuscitation (CPR) duration stratified by initial shockable rhythm (A), witnessed cardiac arrest (B), bystander CPR (C), and quartile (Q) of elapsed interval from 9-1-1 dispatch to onset of professional resuscitation (D).

necessary to implement E-CPR within the therapeutic window. However, the challenges of providing quality CPR during transport may reduce survival for those who would have achieved ROSC with further on-scene resuscitation. Considering the trajectory of the curves in Figures 2 through 4, 50% of subjects with an eventual mRS score of 0 to 3 at hospital discharge had achieved ROSC by ≈8 minutes and 90% of subjects by ≈20 minutes. The likelihood of accruing additional cases with an eventual mRS score of 0 to 3 beyond 20 minutes fell to ≈1% to 15%, depending on subject phenotype. Taken together, these data suggest that 8 to 20 minutes of professional resuscitation is a reasonable window to mobilize toward E-CPR. This time frame may shift forward or backward, depending on patient phenotype (ie, shockable initial cardiac rhythm, witnessed cardiac arrest, bystander CPR). In those who achieve ROSC rapidly with traditional CPR, mobilization of novel therapy can be discontinued. Grunau et al[34] found similar results in a regional cohort of 1206 hypothetical E-CPR–eligible subjects: 16 minutes of professional on-scene resuscitation best balanced the risks and benefits of early versus later transport.

Nagao et al[12] calculated the minimum duration of prehospital resuscitation efforts among bystander-witnessed OHCA to achieve ≥99% sensitivity for favorable 30-day neurological outcome in a nationwide, population-based Japanese registry. Depending on the phenotype (shockable initial cardiac rhythm and bystander resuscitation), they concluded that prehospital resuscitation efforts should be continued for at least 40 to 45 minutes in all adults with bystander-witnessed OHCA. They also found a steady decline in the likelihood of favorable outcomes with increasing duration of resuscitation (adjusted OR, 0.84; 95% CI, 0.83–0.84). Our findings from a North American clinical trial data set are remarkably consistent despite important differences in study design and setting. Whereas Nagao et al included only subjects with bystander-witnessed OHCA, we included all subjects with attempted professional resuscitation, regardless

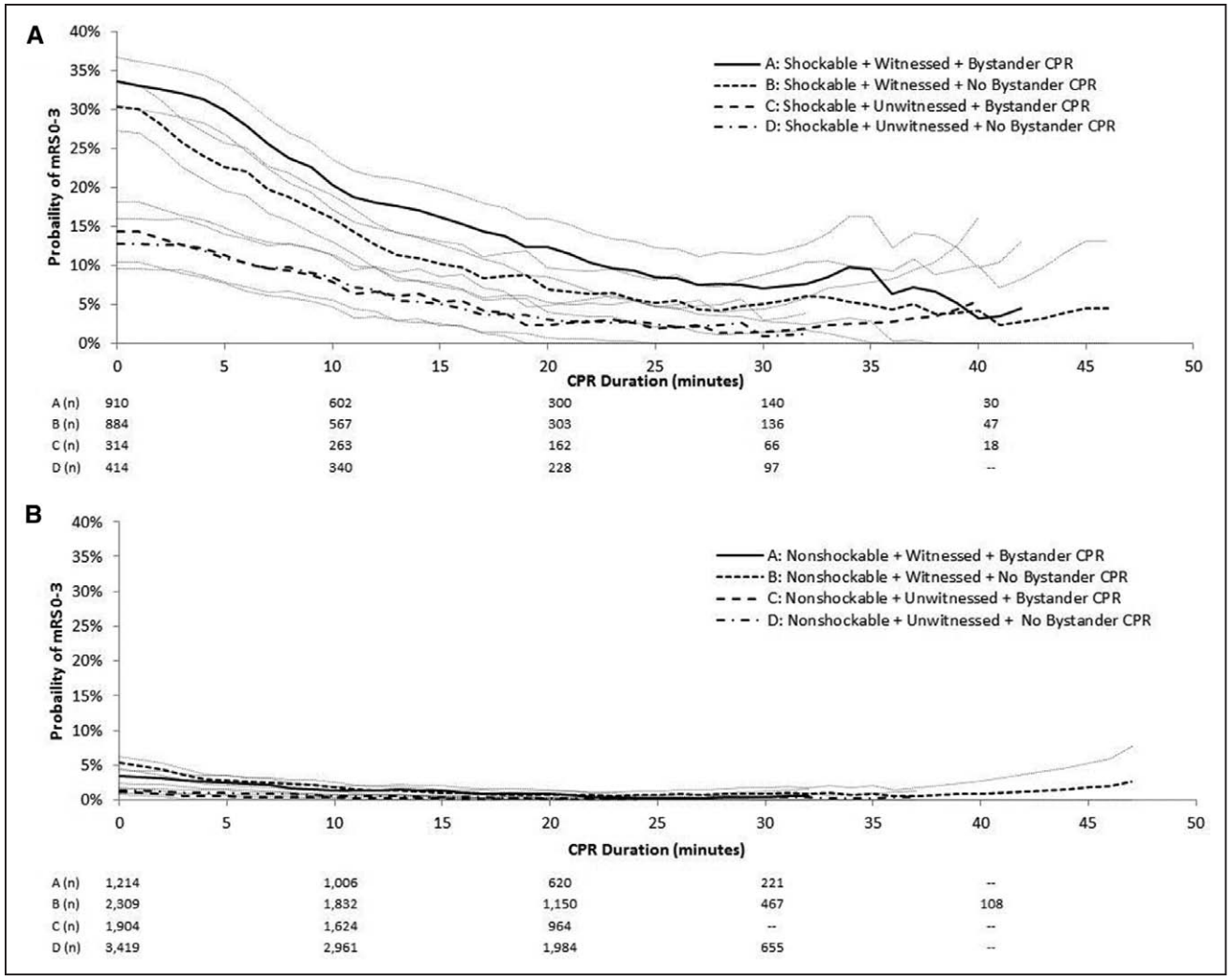

Figure 4. Dynamic probability (black lines) with 95% confidence intervals (gray lines) of survival to hospital discharge with modified Rankin Scale (mRS) score of 0 to 3 as a function of cardiopulmonary resuscitation (CPR) duration for those with (A) and without (B) shockable initial cardiac rhythms stratified by patient phenotype with different combinations of case features.

of witnessed status. We were also able to account for some degree of CPR quality (CPR fraction) and post–cardiac arrest care (therapeutic hypothermia and cardiac catheterization). Furthermore, prehospital providers in Japan must continue resuscitation efforts until ROSC or hospital arrival; they are not legally permitted to terminate resuscitation efforts in the field.[35] On one hand, this setting is ideal to observe the relationship between resuscitation duration and outcomes without confounding elements of TOR practices. However, unlike Japan, most of the world incorporates some form of TOR to reduce futile transport to hospital. Therefore, our data are useful for generalizability to other countries. Similar to Nagao et al, we found that 42.0 minutes (95% CI, 40.5–45.0) of professional resuscitation accrued 99% of all survivors and 37.0 minutes (95% CI, 34.9–40.9 minutes) accrued 99% of those with favorable functional outcome (Figure 2). We also identified a similar decline in probability of favorable functional outcome over elapsed duration of professional resuscitation (adjusted OR, 0.93; 95% CI, 0.92–0.95).

Limitations

The deidentified nature of this data set rendered it impossible to make site-specific comparisons or to adjust for regional variability or clustering. We know there is variation in patient features and survival between ROC sites.[36] Some subjects were transported to hospital during ongoing resuscitation; it is unknown if this affected the likelihood of favorable outcome. Furthermore, no data describe subject comorbidities, degree of post–cardiac arrest illness severity, inpatient prognostication, and other care processes associated with clinical outcomes (oxygenation, ventilation, hemodynamic management, glycemic control, etc). However, the advantage of these

Table 2. Unadjusted and Adjusted Logistic Regression Models for an mRS Score of 0 to 3 on Hospital Discharge

	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Prehospital model (c statistic, 0.93)				
CPR duration	0.87 (0.86–0.87)	<0.0001	0.93 (0.92–0.95)	<0.0001
Age	0.97 (0.96–0.97)	<0.0001	0.95 (0.94–.96)	<0.0001
Male sex	1.73 (1.48–2.02)	<0.0001	1.23 (0.88–1.71)	0.22
Witnessed arrest (EMS or bystander)	5.72 (4.82–6.80)	<0.0001	2.26 (1.62–3.15)	<0.001
Bystander CPR	1.42 (1.24–1.63)	<0.0001	0.89 (0.66–1.18)	0.41
Dispatch to first professional CPR	1.01 (1.01–1.02)	0.002	0.94 (0.91–0.98)	0.002
Shockable initial rhythm	13.51 (11.55–15.82)	<0.0001	13.66 (9.67–19.29)	<0.0001
Mean CCF first 10 min	0.09 (0.06–0.15)	<0.0001	1.38 (0.53–3.63)	0.51
Advanced airway attempted	0.66 (0.57–0.77)	<0.0001	0.64 (0.35–1.16)	0.14
Epinephrine administered	0.13 (0.11–0.15)	<0.0001	0.68 (0.61–0.76)	<0.0001
Inpatient model (c statistic, 0.91)				
CPR duration	0.90 (0.89–0.91)	<0.0001	0.97 (0.95–0.99)	0.04
Age	0.97 (0.96–0.97)	<0.0001	0.96 (0.95–0.97)	<0.0001
Male sex	1.77 (1.50–2.10)	<0.0001	1.22 (0.81–1.84)	0.35
Witnessed arrest (EMS or bystander)	2.51 (2.08–3.03)	<0.0001	1.61 (1.07–2.42)	0.02
Bystander CPR	1.19 (1.02–1.39)	0.03	0.77 (0.54–1.11)	0.17
Dispatch to first professional CPR	1.01 (1.01–1.02)	0.04	0.93 (0.88–0.97)	0.003
Shockable initial rhythm	6.27 (5.28–7.45)	<0.0001	3.69 (2.38–5.72)	<0.001
Mean CCF first 10 min	0.15 (0.09–0.26)	<0.0001	0.83 (0.26–2.69)	0.76
Advanced airway attempted	0.38 (0.32–0.46)	<0.0001	0.36 (0.13–0.99)	0.04
Epinephrine administered	1.13 (0.11–0.16)	<0.0001	0.85 (0.75–0.96)	0.01
Therapeutic hypothermia	1.34 (1.15–1.57)	<0.0001	1.51 (0.99–2.29)	0.06
Cardiac catheterization	12.41 (10.12–15.22)	<0.0001	7.63 (5.14–11.35)	<0.001

CCF indicates chest compression fraction; CI, confidence interval; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OR, odds ratio.

trial data (as opposed to self-reported registry data) is the high degree of accuracy, especially in prehospital time-stamped data,[37] and structured, prospective outcome assessment. We note that many subjects did not have complete time-stamped data (Figure 1). Summary features of excluded subjects were comparable to those of included subjects. Finally, the elapsed interval from 9-1-1 call to onset of professional resuscitation is a best estimate of ischemic insult but does not capture the full magnitude of no-flow time for subjects with unwitnessed cardiac arrest or delays in activation of the emergency response system. Likewise, it does not capture the presence or quality of bystander resuscitation attempts.

CONCLUSIONS

Each elapsed minute of resuscitation is independently associated with lower odds of favorable functional outcome at hospital discharge. However, those with favorable case features (shockable initial cardiac rhythm, bystander CPR, witnessed cardiac arrest) were more likely to survive with favorable functional outcome after longer resuscitations and warrant early consideration of novel therapies such as E-CPR. Resuscitation duration in the absence of ROSC should not be used as an ad hoc criterion for TOR. In the present model of OHCA resuscitation in North America, few are likely to have favorable outcome after 47 minutes of CPR.

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FOOTNOTES

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Association Between Duration of Resuscitation and Favorable Outcome After Out-of-Hospital Cardiac Arrest: Implications for Prolonging or Terminating Resuscitation

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SUPPLEMENTAL MATERIAL

Shockable initial cardiac rhythm	Non-shockable initial cardiac rhythm	p-value
16.0 (8.8-26.0)	20.8 (13.0-27.8)	<0.00001

Witnessed cardiac arrest	Unwitnessed cardiac arrest	p-value
18.0 (10.0-27.0)	21.0 (14.0-28.6)	<0.00001

Bystander CPR	No bystander CPR	p-value
19.0 (11.7-26.4)	20.3 (12.0-28.0)	<0.00001

Quartile 1: 911 dispatch to onset CPR	Quartile 2: 911 dispatch to onset CPR	Quartile 3: 911 dispatch to onset CPR	Quartile 4: 911 dispatch to onset CPR	p-value
19.6 (11.7-27.0)	20.0 (12.8-27.6)	20.7 (12.3-28.0)	19.1 (11.0-26.9)	<0.00001

Shockable initial cardiac rhythm + witnessed cardiac arrest + bystander CPR	Shockable initial cardiac rhythm + witnessed cardiac arrest	Shockable initial cardiac rhythm + bystander CPR	Witnessed cardiac arrest + bystander CPR	Non-shockable initial cardiac rhythm + unwitnessed cardiac arrest + no bystander CPR	p-value
13.7 (8.0-23.6)	18.4 (10.1-27.2)	18.5 (10.9-26.4)	18.8 (11.0-27.0	20.2 (12.5-34.0)	<0.00001

Supplemental Table: Median (IQR) durations of CPR for subject phenotypes compared with Wilcoxon rank-sum test or Kruskall-Wallis test. **IQR**: inter-quartile range.