ANESTHESIOLOGY

Delays in Cardiopulmonary Resuscitation, Defibrillation, and Epinephrine Administration All Decrease Survival in In-hospital Cardiac Arrest

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ABSTRACT

Background: Because the extent to which delays in initiating cardiopulmonary resuscitation (CPR) *versus* the time from CPR to defibrillation or epinephrine treatment affects survival remains unknown, it was hypothesized that all three independently decrease survival in in-hospital cardiac arrest.

Methods: Witnessed, index cases of cardiac arrest from the Get With The Guidelines–Resuscitation Database occurring between 2000 and 2008 in 538 hospitals were included in this analysis. Multivariable risk-adjusted logistic regression examined the association of time to initiation of CPR and time from CPR to either epinephrine treatment or defibrillation with survival to discharge.

Results: In the overall cohort of 57,312 patients, there were 9,802 survivors (17.1%). Times to initiation of CPR greater than 2 min were associated with a survival of 14.7% (91 of 618) as compared with 17.1% (9,711 of 56,694) if CPR was begun in 2 min or less (adjusted odds ratio [95% CI], 0.68 [0.54 to 0.87]; $P < 0.002$). Times from CPR to either defibrillation or epinephrine treatment of 2 min or less were associated with a survival of 18.0% (7,654 of 42,475), as compared with 15.0% (1,680 of 11,227) for 3 to 5 min (reference, 0 to 2 min; adjusted odds ratios [95% CI], 0.83 [0.78 to 0.88]; $P < 0.001$), 12.8% (382 of 2,983) for 6 to 8 min (0.67 [0.60 to 0.76], $P < 0.001$), and 13.7% (86 of 627) for 9 to 11 min (0.54 [0.42 to 0.69], $P < 0.001$).

Conclusions: Delays in the initiation of CPR and from CPR to defibrillation or epinephrine treatment were each associated with lower survival.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Rapid response to witnessed, pulseless cardiac arrest is associated with increased survival.

What This Article Tells Us That Is New

- Assessment of witnessed, pulseless cardiac arrests occurring at 538 hospitals during a 9-yr period indicates that CPR did not occur immediately at 0 min in 5.7% of patients despite guidelines for instantaneous initiation. Delay in initiation of CPR was associated with significantly decreased survival.
- Time to initiation of CPR and subsequent time to initiation of administration of defibrillation shock (for shockable arrhythmias) and epinephrine were both associated with reduced patient survival.

Although in-hospital cardiac arrest is a common event in U.S. hospitals, survival remains as low as about 20%.[1,2] Prior studies for out-of-hospital cardiac arrests have emphasized the critical importance of prompt initiation of cardiopulmonary resuscitation (CPR). Others have documented the importance of prompt treatment with defibrillation for patients with shockable in-hospital cardiac arrest[3] and with epinephrine for those with nonshockable in-hospital cardiac arrest.[4] However, the relationship between time to initiation of CPR and survival for in-hospital cardiac arrest is not well understood. Moreover, the total time between pulselessness and defibrillation or epinephrine treatment comprises both time to initiation of CPR and time from CPR to either treatment. The effect on survival of each of these intervals has not been previously characterized.

Accordingly, we examined the association between time to initiation of CPR and time from CPR to either defibrillation or epinephrine treatment on in-hospital cardiac arrest outcomes using data from Get With The Guidelines–Resuscitation, a large prospective, hospital-based, multicenter clinical registry that uses standardized definitions to

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assess both care processes and outcomes.[5] We hypothesized that delays in the initiation of CPR and from time of CPR to defibrillation or epinephrine treatment are each associated with lower in-hospital cardiac arrest survival.

Materials and Methods

Patient Population

The Get With The Guidelines–Resuscitation (formerly known as the National Registry of Cardiopulmonary Resuscitation) is an American Heart Association–sponsored prospective multicenter observational registry of in-hospital cardiac arrest. The design of the Get With The Guidelines–Resuscitation database has been previously described.[2] Briefly, all patients with cardiac arrest (defined as the absence of a palpable central pulse, apnea, and unconsciousness) and without do-not-resuscitate orders are enrolled by hospital quality improvement personnel who have received specialized training. Patients eligible for enrollment are identified from multiple sources, including but not limited to cardiac arrest flow sheets, hospital paging system logs, and routine checks of code carts. Standardized reporting using Utstein-style definitions[5] are used for patient variables and outcomes. This study was approved by the Institutional Review Board of the University of Pittsburgh, Pittsburgh, Pennsylvania. Our statistical analysis plan was approved the National Registry of Cardiopulmonary Resuscitation Adult Research Task Force on April 9, 2009, before accessing the data. This analysis and manuscript were approved by the Executive Database Steering Committee in accordance with the Get With The Guidelines Publication Policy.[6]

Between 2000 and 2008, we identified 132,950 patients with an in-hospital cardiac arrest within Get With The Guidelines–Resuscitation with complete comorbidity data for our model. We excluded 21,212 episodes of recurrent arrest to focus on index in-hospital cardiac arrest events (fig. 1). As we evaluated the effect of time to initiation of CPR on outcomes, we excluded 21,334 patients with an unwitnessed in-hospital cardiac arrest and 6,998 patients without information on time to initiation of CPR. We also excluded 5,549 patients with implausible time to initiation of CPR (*i.e.*, negative times [n = 5,036] and time to initiation of CPR of 7 min or more [n = 513]). Our study population comprised 77,857 patients with a witnessed in-hospital cardiac arrest with time to initiation of CPR of 0 to 6 min. We excluded 8,954 patients for missing values for times from CPR to defibrillation or epinephrine treatment. We also excluded patients missing survival data and for negative or outlier times from CPR to defibrillation or epinephrine treatment (11,528 excluded patients, outliers as defined by Tukey box plot of more than 11 min in the defibrillation group or more than 9 min in the epinephrine group). The final sample sizes were 11,002 in the defibrillation group and 46,310 in the epinephrine group.

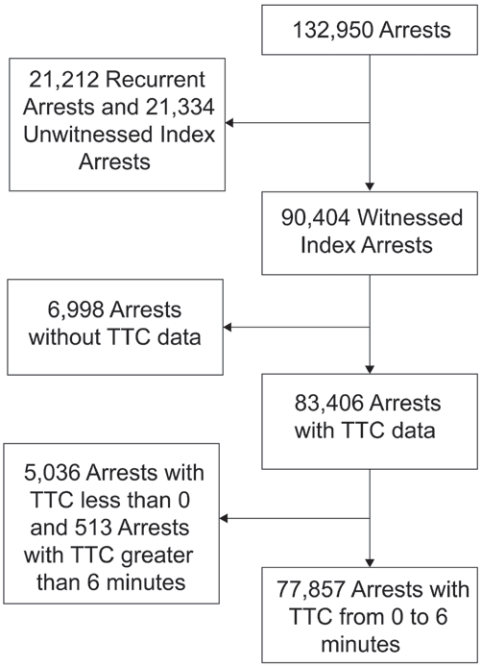

Fig. 1. Study cohort selection. TTC, time to initiation of cardiopulmonary resuscitation.

Independent Variables and Study Outcomes

Our two main independent variables were established *a priori* and were (1) time to initiation of CPR and (2) time from the initiation of CPR to treatment, defined as either defibrillation or epinephrine. Time to initiation of CPR was defined as the difference between the recorded clock time for the determination of pulselessness and the recorded clock time for the beginning of chest compressions. Similarly, because we aimed to study the influence of delay (as opposed to the influence of shockable *vs.* nonshockable rhythms), time to treatment was defined as the difference between the recorded clock time for either the first defibrillation attempt or the administration of epinephrine and time for initiation of CPR. For patients who received both defibrillation and epinephrine treatments, this interval was defined by whichever intervention was recorded as being given first. Survival to discharge was established *a priori* as our primary outcome.

Statistical Analysis

Baseline differences between the defibrillation- and epinephrine-treated groups were examined. Continuous variables were compared with the median and Kruskal–Wallis

Table 1. Selected Group Baseline Characteristics

Characteristic	All Patients (n = 57,312)	DEF Group (n = 11,002)	EPI Group (n = 46,310)	Between-Groups *P* Value
Age, yr, median (interquartile range)	67 (54,78)	67 (56,77)	68 (54,78)	0.002
Men	33,331 (58.2)	6,877 (62.5)	26,454 (57.1)	< 0.001
White race	40,130 (70.0)	8,309 (75.5)	31,821 (68.7)	< 0.001
Shockable rhythm	11,822 (20.6)	9,134 (83.0)	2,688 (5.8)	< 0.001
Intensive care unit	34,935 (61.0)	6,123 (55.7)	28,812 (62.2)	< 0.001
Automatic external defibrillator used	4,799 (8.9)	1,183 (10.8)	3,616 (7.8)	< 0.001
Illness category				< 0.001
Medical				
Cardiac	21,453 (37.4)	5,710 (51.9)	15,743 (34.0)	
Noncardiac	22,788 (39.8)	2,768 (25.2)	20,020 (43.2)	
Surgical				
Cardiac	4,673 (8.2)	1,372 (12.5)	3,301 (7.1)	
Noncardiac	6,047 (10.6)	927 (8.4)	5,170 (11.2)	
Arrhythmia	20,651 (36.0)	5,000 (45.4)	15,651 (33.8)	< 0.001
Baseline CNS dysfunction	7,776 (13.6)	1,168 (10.6)	6,608 (14.3)	< 0.001
Congestive heart failure				
This admission	11,183 (19.5)	2,502 (22.7)	8,681 (18.7)	< 0.001
Prior admission	12,344 (21.5)	2,694 (24.5)	9,650 (20.8)	< 0.001
Diabetes mellitus	16,394 (28.6)	3,230 (29.4)	13,164 (28.4)	0.050
Hypotension	19,970 (34.8)	2,990 (27.2)	16,980 (36.7)	< 0.001
Metastatic malignancy	6,569 (11.5)	839 (7.6)	5,730 (12.4)	< 0.001
Metabolic/electrolyte abnormality	11,566 (20.2)	1,743 (15.8)	9,823 (21.2)	< 0.001
Acute myocardial infarction, this admission	11,838 (20.7)	3,556 (32.3)	8,282 (17.9)	< 0.001
Myocardial infarction, prior admission	10,293 (18.0)	2,691 (24.5)	7,602 (16.4)	< 0.001
Pneumonia	7,818 (13.6)	1,005 (9.1)	6,813 (14.7)	< 0.001
Renal insufficiency	19,411 (33.9)	3,186 (28.9)	16,225 (35.0)	< 0.001
Respiratory insufficiency	27,385 (47.8)	4,025 (36.6)	23,360 (50.5)	< 0.001
Sepsis	9,665 (16.9)	1,179 (10.7)	8,486 (18.3)	< 0.001
Mechanical ventilation	23,069 (40.3)	3,799 (34.5)	19,270 (41.6)	< 0.001
Arterial catheter	7,372 (12.9)	1,520 (13.8)	5,852 (12.6)	0.001
Dopamine infusion	11,815 (20.6)	1,835 (16.7)	9,980 (21.6)	< 0.001
Norepinephrine infusion	8,039 (14.0)	997 (9.1)	7,042 (15.2)	< 0.001

Values are n (%), unless otherwise specified. For a complete list, see supplemental table 2 (http://links.lww.com/ALN/B829), which lists all group baseline covariates in the model.
CNS, central nervous system; DEF group, patient group treated with defibrillation; EPI group, patient group treated with epinephrine.

tests, and categorical variables were compared using the chi-square test.

We then constructed multivariable logistic regression models to examine the associations between survival as an outcome and time to initiation of CPR and time from CPR to defibrillation or epinephrine treatment as ordinal categorical predictors. To maximize statistical power and to allow comparison of the two groups, we developed models in which the groups were combined, as well as separate models for each group. To further enhance statistical power, in *post hoc* exploratory analysis, we evaluated various binning strategies (supplemental table 1, http://links.lww.com/ALN/B828, describing the partitioning of categories for each binning strategy) in addition to univariate and pointwise analysis for time to initiation of CPR and time to treatment. We dichotomized time to initiation of CPR into ranges of 0 to 2 and 3 to 6 min. We also categorized time to defibrillation and time to epinephrine treatment into ranges 0 to 2, 3 to 5, 6 to 8, and 9 to 11 min.

After screening study variables for collinearity, we included the following covariates in our model: age, sex, race, whether the patient was monitored, location of cardiac arrest, initial rhythm, illness category (medical cardiac, medical noncardiac, surgical cardiac, surgical noncardiac), and comorbidities present within 24 h of cardiac arrest (table 1; supplemental table 2, http://links.lww.com/ALN/B829, depicting a complete list of group baseline characteristics). Moreover, we included in the model interventions in place at the time of cardiac arrest, including mechanical ventilation, various vasopressors, and other invasive procedures (supplemental table 2, http://links.lww.com/ALN/B829, depicting a complete list of group baseline characteristics). In *post hoc* testing, we assessed possible clustering effects at the hospital level (*i.e.*, between hospitals) in three separate analyses: (1) adding facility as a covariate to our model, (2) our model using the generalized estimating equation (details in supplemental table 3, http://links.lww.com/ALN/B830, detailing model evaluation), and (3) a two-stage hierarchical analysis using facility and location (within the hospital), as

well as the other covariates in our model. We also did *post hoc* sensitivity analysis by excluding patients who received defibrillation for a nonshockable rhythm or epinephrine for a shockable rhythm. In addition, we performed fractional polynomial analysis and logistic regression diagnostics using Stata/SE 15.1 (StataCorp LLC, USA). All other analyses were conducted using SPSS 22 to 25 (IBM SPSS, USA) and were assessed at a two-sided significance level of 0.05.

Results

Demographic Data

Selected baseline characteristics of the patient groups treated with defibrillation and epinephrine are provided in table 1 (for a complete list see supplemental tables 2 and 4, http://links.lww.com/ALN/B829 and http://links.lww.com/ALN/B831, depicting a complete list of group baseline characteristics and their influence on survival, respectively). The median age in the overall cohort was 67 yr (interquartile range, 54, 78), 70.0% (40,130 of 57,312) were of white race; for 61.0% (34,935 of 57,312), in-hospital cardiac arrest occured in an intensive care unit. Of 57,312 patients, 44,241 were medical (77.2%) and 10,720 (18.7%) were surgical. Of patients treated initially with epinephrine, 94.3% (43,622 of 46,310) had a nonshockable cardiac arrest rhythm, whereas 83.0% (9,134 of 11,002) of defibrillated patients had a shockable cardiac arrest rhythm. A greater proportion of the epinephrine-treated group (table 1) were hypotensive at the time of cardiac arrest (defibrillation group 27.2% [2,990 of 11,002] *vs.* epinephrine group 36.7% [16,980 of 46,310]), had respiratory insufficiency (defibrillation group 36.6% [4,025 of 11,002] *vs.* epinephrine group 50.5% [23,360 of 46,310]), or required mechanical ventilation (defibrillation group 34.5% [3,799 of 11,002] *vs.* epinephrine group 41.6% [19,270 of 46,310]). The results of our exploratory analysis are presented in supplemental table 3 (http://links.lww.com/ALN/B830, detailing model evaluation), supplemental table 5 (http://links.lww.com/ALN/B832, detailing univariate analysis), supplemental tables 6–13 (http://links.lww.com/ALN/B833, http://links.lww.com/ALN/B834, http://links.lww.com/ALN/B835, http://links.lww.com/ALN/B836, http://links.lww.com/ALN/B837, http://links.lww.com/ALN/B838, http://links.lww.com/ALN/B839, http://links.lww.com/ALN/B840), and supplemental figs. 1 and 2 (http://links.lww.com/ALN/B841 and http://links.lww.com/ALN/B842, depicting multivariable pointwise analysis).

Overall Cohort (Groups Combined)

In our combined model, after multivariable adjustment, increasing time to initiation of CPR and time from CPR to treatment were associated with decreased survival (table 2). In the overall cohort of 57,312 patients, there were 9,802 survivors (17.1%; table 3). Times to initiation of CPR greater than 2 min were associated with a survival of 14.7% (91 of 618) as compared with 17.1% (9,711 of 56,694) if CPR was begun in 2 min or less (adjusted odds ratio [CI], 0.68 [0.54 to 0.87]; $P < 0.002$; table 2; fig. 2). Times from CPR to either defibrillation or epinephrine treatment of 2 min or less were associated with a survival of 18.0% (7,654 of 42,475), as compared with 15.0% (1,680 of 11,227) for 3 to 5 min, 12.8% (382 of 2,983) for 6 to 8 min, and 13.7% (86 of 627) for 9 to 11 min (reference, 0 to 2 min; for 3 to 5 min adjusted odds ratio, 0.83; CI, 0.78 to 0.88; $P < 0.001$, for 6 to 8 min adjusted odds ratio, 0.67; CI, 0.60 to 0.76; $P < 0.001$, and for 9 to 11 min adjusted odds ratio, 0.54; CI, 0.42 to 0.69; $P < 0.001$; table 2; fig. 3). There was a substantial difference between groups not only with respect to survival (38% [4,178 of 11,002] for patients treated with defibrillation *vs.* 12.1% [5,624 of 46,310] for patients treated with epinephrine, adjusted odds ratio, 0.41; CI, 0.37 to 0.44; $P < 0.001$; tables 2 and 3), but also in the rate at which survival is diminished with respect to time from CPR to either defibrillation or epinephrine therapy (overall effect $P < 0.001$, reference 0 to 2 min, for 3 to 5 min adjusted odds ratio, 0.66; CI, 0.59 to 0.75; $P < 0.001$, for 6 to 8 min adjusted odds ratio, 0.44; CI, 0.34 to 0.55; $P < 0.001$, and for 9 to 11 min, adjusted odds ratio, 0.31; CI, 0.25 to 0.44; $P < 0.001$; tables 2 and 3; supplemental figs. 4 and 6, http://links.lww.com/ALN/B844 and http://links.lww.com/ALN/B846, depicting the stepwise reduction in survival with increasing time to defibrillation and epinephrine treatment, respectively). This same model was tested using the generalized estimating equation and yielded very similar results (details in supplemental table 3, http://links.lww.com/ALN/B830, detailing model evaluation).

Defibrillation Group

If CPR was begun in 2 min or less, survival was 38.1% (4,143 of 10,880) as compared with 28.7% (35 of 122) if CPR was begun in 3 to 6 min (adjusted odds ratio, 0.60; CI, 0.39 to 0.93, $P = 0.023$; table 2; supplemental fig. 3, http://links.lww.com/ALN/B843, depicting the reduction in survival with delayed CPR). Similarly, if defibrillation was attempted in 2 min or less, survival was 40.5% (3,530 of 8,713), as compared with 31.6% (508 of 1,608) at 3 to 5 min, 22.4% (100 of 447) at 6 to 8 min, and 17.1% (40 of 234) at 9 to 11 min (adjusted odds ratio, 0.79; CI, 0.69 to 0.90 for 3 to 5 min, adjusted odds ratio, 0.67; CI, 0.52 to 0.87 for 6 to 8 min, adjusted odds ratio, 0.51; CI, 0.35 to 0.75, overall effect; $P < 0.001$; table 2; supplemental fig. 4, http://links.lww.com/ALN/B844, depicting the decrease in survival with delayed defibrillation). If CPR and defibrillation were both delivered promptly (*i.e.*, within 2 min), survival was 40.6% (3,503 of 8,628; table 3). If CPR was begun promptly, but defibrillation was delayed (followed CPR by more than 3 min), survival was 31.9% (504 of 1,582) for 3- to 5-min delay, 21.9% (97 of 442) for 6- to 8- min

Table 2. Association between Treatment Times and Survival

	Observed			Adjusted Analysis	
	N	Survivors	Survival Probability	Odds Ratio (CI)	*P* Value
Overall cohort (DEF and EPI groups combined)					
Time to initiation of CPR					
0–2	56,694	9,711	0.171	Reference	
3–6	618	91	0.147	0.68 (0.54–0.87)	0.002
Time from CPR to defibrillation or epinephrine treatment (overall effect $p < 0.0005$)					
0–2	42,475	7,654	0.180	Reference	
3–5	11,227	1,680	0.150	0.83 (0.78–0.88)	< 0.001
6–8	2,983	382	0.128	0.67 (0.60–0.76)	< 0.001
9–11	627	86	0.137	0.54 (0.42–0.69)	< 0.001
Between groups				0.41 (0.37–0.44)	< 0.001
DEF group					
Time to initiation of CPR					
0–2	10,880	4,143	0.381	Reference	
3–6	122	35	0.287	0.60 (0.39–0.93)	0.023
Time from CPR to defibrillation (overall effect $p < 0.001$)					
0–2	8,713	3,530	0.405	Reference	
3–5	1,608	508	0.316	0.79 (0.69–0.90)	< 0.001
6–8	447	100	0.224	0.67 (0.52–0.87)	0.002
9–11	234	40	0.171	0.51 (0.35–0.75)	0.001
EPI group					
Time to initiation of CPR					
0–2	45,814	5,568	0.122	Reference	
3–6	496	56	0.113	0.75 (0.56–1.00)	0.051
Time from CPR to epinephrine treatment (overall effect $p < 0.001$)					
0–2	33,762	4,124	0.122	Reference	
3–5	9,619	1,172	0.122	0.88 (0.82–0.95)	0.001
6–9	2,929	328	0.112	0.75 (0.66–0.85)	< 0.001

Longer times to CPR and delays in time from CPR initiation to defibrillation or epinephrine treatments were associated with lower survival. The results are shown for the overall cohort and separately for patients receiving either defibrillation or epinephrine treatment. Interaction terms: group by time to initiation of CPR, adjusted odds ratio (CI) 1.22 (0.73 to 2.02), $P = 0.445$; group by time from CPR, overall effect $P < 0.001$, group by time from CPR 0 to 2 min, reference; group by time from CPR 3 to 5 min, adjusted odds ratio (CI) 0.66 (0.59 to 0.75), $P < 0.001$; group by time from CPR 6 to 8 min, adjusted odds ratio (CI) 0.44 (0.34 to 0.55), $P < 0.001$; and group by time from CPR 9 to 11 min, adjusted odds ratio (CI) 0.31 (0.25 to 0.44), $P < 0.001$. All times are expressed in minutes.

CPR, cardiopulmonary resuscitation; DEF group, patient group treated with defibrillation; EPI group, patient group treated with epinephrine.

delay, and 17.1% (39 of 228) for 9- to 11-min delay (table 3). If CPR was delayed (*i.e.*, begun after 3 to 6 min), survival was reduced to 31.8% (27 of 85) if defibrillation followed CPR by 0 to 2 min and 15.4% (4 of 26) if defibrillation followed CPR by 3 to 5 min (table 3).

Epinephrine Group

There was no difference in survival between patients who received CPR in 3 to 6 min (11.3% [56 of 496]) as compared with within 2 min (12.2% [5,568 of 45,814]; adjusted odds ratio, 0.75; CI, 0.56 to 1.00; $P = 0.051$; table 2; supplemental fig. 5, http://links.lww.com/ALN/B845, depicting survival with prompt *vs.* delayed CPR). There was a stepwise reduction in survival with each additional interval of delay from the initiation of CPR to epinephrine treatment: if epinephrine was administered within 2 min of initiation of CPR, survival was 12.2% (4,124 of 33,762) as compared with 12.2% (1,172 of 9,619; adjusted odds ratio, 0.88; CI, 0.82 to 0.95; $P = 0.001$) for 3 to 5 min and 11.2% (328 of 2,929; adjusted odds ratio, 0.75; CI, 0.66 to 0.85; $P < 0.001$; table 2; supplemental fig. 6, http://links.lww.com/ALN/B846, depicting the reduction in survival with increasing delay in epinephrine treatment). If both CPR and epinephrine were delivered promptly, survival was 12.2% (4,078 of 33,402), and if epinephrine was delayed by 3 to 5 or 6 to 9 min, survival was 12.2% (1,163 of 9,516) or 11.3% (327 of 2,896), respectively (table 3). If CPR was delayed (more than 2 min), survival was 12.8 (46 of 360), 8.7 (9 of 103), and 3.0% (1 of 33) for times to epinephrine of 0 to 2, 3 to 5, and 6 to 9 min, respectively (table 3).

Discussion

Our study contains several novel results. First, the frequency of delay between the confirmation of pulselessness and the initiation of CPR was greater than our *a priori* expectation that CPR would begin immediately. We found that 5.7% (3,283

Table 3. Survival Stratified by Treatment Times

	Time to Initiation of CPR					
	0–2 min			3–6 min		
TFC, min	N	Survivors	%	N	Survivors	%
Overall cohort						
0–2	42,030	7,581	18.0	445	73	16.4
3–5	11,098	1,667	15.0	129	13	10.1
6–8	2,950	378	12.8	33	4	12.1
9–11	616	85	13.8	11	1	9.1
DEF group						
0–2	8,628	3,503	40.6	85	27	31.8
3–5	1,582	504	31.9	26	4	15.4
6–8	442	97	21.9	5	3	60.0
9–11	228	39	17.1	6	1	16.7
EPI group						
0–2	33,402	4,078	12.2	360	46	12.8
3–5	9,516	1,163	12.2	103	9	8.7
6–9	2,896	327	11.3	33	1	3.0

The results are shown for the overall cohort and separately for patients receiving either defibrillation or epinephrine treatment. Within the entire cohort, time to initiation of CPR ranged from 0 to 6 min, with a median of 0 (interquartile range, 0 to 0 min). Cardiopulmonary resuscitation was initiated immediately upon identification of an in-hospital cardiac arrest (time to initiation of CPR of 0) in 94.3% (54,029 of 57,312) of patients (supplemental tables 6 and 7, http://links.lww.com/ALN/B833 and http://links.lww.com/ALN/B834, depicting pointwise multivariable analysis). Among patients treated with defibrillation (defibrillation group, n = 11,002), time from the initiation of CPR to first defibrillation ranged from 0 to 11 min with median 0 (interquartile range, 0, 2; supplemental table 8, http://links.lww.com/ALN/B835, depicting pointwise multivariable analysis). In addition, 98.9% (10,880 of 11,002) had CPR begun within 2 min of identification of cardiac arrest, with 10,257 (93.2%) having time to initiation of CPR of 0 min (supplemental table 6, http://links.lww.com/ALN/B833, depicting the pointwise survival for time to initiation of CPR). Similarly, 79.2% (8.713 of 11,002) were defibrillated within 2 min from the time of initiation of CPR, 14.6% (1,608 of 11,002) between 3 and 5 min from the time of CPR initiation, and 6.2% (681 of 11,002) were defibrillated after 6 min or more (supplemental table 8, http://links.lww.com/ALN/B835, describing pointwise survival with increasing time from CPR to defibrillation). In contrast, among patients treated with epinephrine (epinephrine group, n = 46,310), time from initiation of CPR to first epinephrine administration ranged from 0 to 9 min with median 1 (interquartile range, 0, 3; supplemental table 9, http://links.lww.com/ALN/B836, depicting pointwise multivariable analysis). For patients treated with epinephrine, 98.9% (45,814 of 46,310) had CPR begun within 2 min after cardiac arrest, with 94.5% (43,772 of 46,310) having times to initiation of CPR of 0 min (supplemental table 7, http://links.lww.com/ALN/B834, describing pointwise survival with increasing time to initiation of CPR). Similarly, 72.9% (33,762 of 46,310) and 20.8% (9,619 of 46,310) of patients received epinephrine within 2 min and 3 to 5 min from the time of initiation of CPR, respectively, and 6.3% (2,929 of 46,310) at 6 min or more (table 3).

CPR, cardiopulmonary resuscitation; DEF group, patient group treated with defibrillation; EPI group, patient group treated with epinephrine; TFC, time from CPR to treatment.

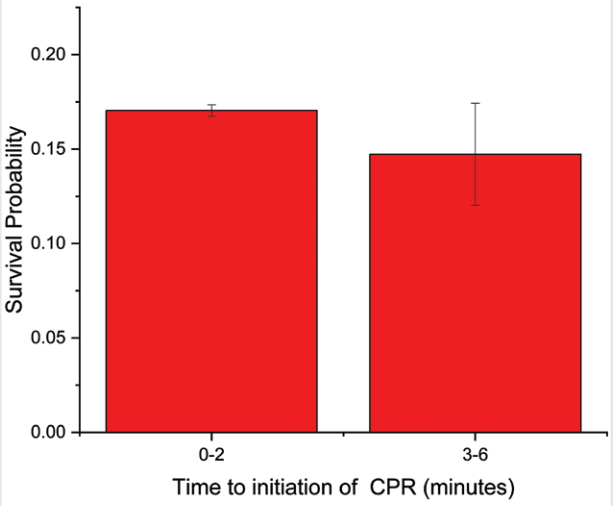

Fig. 2. Survival probability in the overall cohort with increasing time to initiation of cardiopulmonary resuscitation (CPR). *Error bars* represent unadjusted Clopper–Pearson binomial 95% CI.

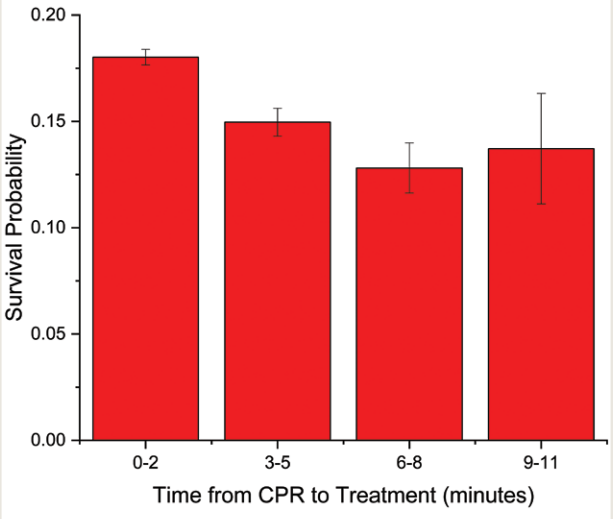

Fig. 3. Survival probability in the overall cohort with increasing time from cardiopulmonary resuscitation (CPR) to treatment. *Error bars* represent unadjusted Clopper–Pearson binomial 95% CI.

of 57,312) of patients did not have instantaneous initiation of CPR upon determination of a pulseless cardiac arrest (*i.e.*, time to initiation of CPR of more than 0 min). Our second and most important finding was that delay in initiation of CPR reduces survival independent of subsequent delays in defibrillation or epinephrine administration. Although several other studies in this database have examined a potential effect of delay in the initiation of CPR,[4,7–10] none have found that effect.

The third novel finding is that both time to initiation of CPR and time from CPR to defibrillation are determinants of survival in patients with shockable in-hospital cardiac arrests. Thus, the expected survival advantage from early CPR can be severely reduced by subsequent delay in defibrillation, *i.e.*, an inefficient resuscitation. Fourth, in the epinephrine group, although the influence of arrest interval[11] and delay in defibrillation[3,12] are well recognized, our analysis is the first to suggest that increasing the time from the initiation of CPR to the administration of epinephrine was associated with lower survival. It is well known that patients in the epinephrine group start with a very poor prognosis as compared with patients in the defibrillation group.[1–4]

Attention to both prompt CPR and prompt epinephrine administration are particularly important for the management of in-hospital cardiac arrest, because pulseless electrical activity and asystole comprise up to 82% of all such arrests.[2,13] Fifth, the rate of decline in survival with time from CPR to therapy is quite large in the defibrillation group as compared with the epinephrine group (table 2; supplemental figs. 4 and 6, http://links.lww.com/ALN/B844 and http://links.lww.com/ALN/B846, depicting the stepwise reduction in survival with increasing time from CPR to defibrillation and epinephrine treatment respectively).

The total time from determination of pulselessness to defibrillation in the setting of ventricular fibrillation has long been known to be a determinant of outcome both for in-hospital[3] and out-of-hospital cardiac arrest.[5,11,14–17] In the pre-hospital setting, as the total time to defibrillation increases, even though survival decreases, relative improvement associated with bystander CPR increases.[18] We observed a similar context sensitivity for in-hospital cardiac arrest, *i.e.*, delay in CPR reduces the survival benefit of defibrillation even if the total time to defibrillation remains the same. Similarly, total time to epinephrine treatment is also known to be a determinant of outcome for out-of-hospital[19,20] as well as in-hospital cardiac arrest both in adults[4] and in children.[10] Our results are consistent with prior studies. The novel feature of our work is the explicit demonstration that after adjustment for time to initiation of CPR, the time from the initiation of CPR to epinephrine treatment is a determinant of survival.

Although there is considerable observational evidence from the prehospital setting that increasing duration of cardiac arrest before CPR lowers survival,[15–17,21] relatively few studies have examined delays in CPR in the in-hospital setting. Herlitz *et al.*[22] reported that if CPR was started within 1 min, survival was 33% as compared with 14% if CPR was started later. Hajbaghery *et al.*[23] reported that in all patients that survived to hospital discharge and all patients on the morning shift, CPR was started in 1 to 6 min. For the evening and night shifts, CPR was started in 1 to 6 min in 92 and 89% of patients, respectively. Survival to hospital discharge was 8.3, 4.8, and 3.6%, respectively, for day, evening, and night shifts. Forcina *et al.*[24] reported that in nursing units using standard defibrillators, median time to initiation of CPR was 0 (interquartile range, 0, 1), but in those units using automatic external defibrillators, median time to initiation of CPR was 0 (interquartile range, 0, 2; $P = 0.08$). Although they found that this trend toward increased time to initiation of CPR did not correlate directly with survival, there was a trend toward decreased survival in the automatic external defibrillator units (18%) as compared with the standard defibrillator units (23%, $P = 0.09$). Although the reported delays in our study are comparable to those in the literature, the use of a large database and risk-adjusted model provides stronger evidence that delay in CPR in in-hospital cardiac arrest decreases survival.

The total time from determination of pulselessness to either the first defibrillation attempt or to epinephrine treatment is a measure of two separate processes. The total time for each includes the time from pulselessness to the initiation of CPR and then the time from CPR initiation to either defibrillation or epinephrine administration. In our study, there was a graded reduction in survival for delays in defibrillation and epinephrine treatment, and the reduction in survival was made worse if CPR was also delayed. Delivery of CPR, defibrillation, and epinephrine treatment are team and system processes, as well as context-sensitive, *i.e.*, the potential benefit of each therapy is partially dependent on the other therapies rendered concurrently or subsequently. Previous analyses have tended to focus on individual therapies rather than consider the relationship between therapies. A well-functioning team, however, will have been trained to provide CPR, defibrillation, and epinephrine administration in a rapid fashion. Reduction of delays requires prompt action, particularly by ward staff while awaiting the arrival of the code response team. We chose a simple performance-based (*i.e.*, time to therapy) model to examine the impact of delays on survival. Although this model has the minor disadvantage of not grouping patients by initial rhythm, the necessary risk adjustment was accomplished by including initial rhythm as a covariate in our model. This model has the advantage that it identifies therapy that does not match the initial rhythm, *i.e.*, defibrillation for nonshockable rhythms and epinephrine for shockable rhythms. Both delays and mismatch of therapy represent opportunities for both research to understand these problems as well as education to ameliorate them.

Limitations of this study include the absence of independent verification of the times recorded, as well as exclusions either because the computed values for times were beyond the range or because of missing values for survival. The lack of synchronization of clocks in hospitals may also lead to errors in times. Our analysis also was not designed to establish causal factors for delays and did not include other unknown factors that may influence timeliness of CPR or defibrillation and epinephrine treatment. These remain areas of active investigation within Get With The Guidelines–Resuscitation. In addition, because of the curvilinear nature of the relationships between delays and survival, the Hosmer–Lemeshow test (supplemental table 3, http://links.lww.com/ALN/B830, detailing model evaluation) suggests that alternative statistical methods might yield a better model fit. Other limitations include lack of extensibility of our results to all hospitals based on the subgroup of hospitals represented in quality improvement registries such as Get With The Guidelines–Resuscitation.

In conclusion, we found that both delays in time to initiation of CPR and time from CPR to treatment with either defibrillation or epinephrine are associated with lower survival for patients with in-hospital cardiac arrest. Further research is needed to determine the impact of both benchmarking and training efforts for in-hospital cardiac arrest focused on accurately measuring and reducing delays in CPR and from CPR to defibrillation or epinephrine administration.

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Competing Interests

The authors declare no competing interests.

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Appendix: Get With The Guidelines–Resuscitation Investigators

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