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Neurologic outcome in comatose patients resuscitated from out-of-hospital cardiac arrest with prolonged downtime and treated with therapeutic hypothermia

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Abstract

Background—Previous reports have shown that prolonged duration of resuscitation efforts in out-of-hospital cardiac arrest (OHCA) is associated with poor neurologic outcome. This concept has recently been questioned with advancements in post-cardiac arrest care including the use of therapeutic hypothermia (TH). The aim of this study was to determine the rate of good neurologic outcome based on the duration of resuscitation efforts in OHCA patients treated with TH.

Methods—This prospective, observational, study was conducted between January 2008 and September 2012. Inclusion criteria consisted of adult non-traumatic OHCA patients who were comatose after return of spontaneous circulation (ROSC) and received TH. The primary endpoint was good neurologic outcome defined as a cerebral performance category score of 1 or 2. Downtime was calculated as the length of time between the patient being recognized as pulseless and ROSC.

Results—105 patients were treated with TH and 19 were excluded due to unknown downtime, leaving 86 patients for analysis. The median downtime was 18.5 (10.0–32.3) minutes and 33 patients (38.0%) had a good neurologic outcome. When downtime was divided into four groups (≤10 min, 11-20 min, 21-30 min, > 30 min), good neurologic outcomes were 62.5%, 37%, 25%, and 21.7%, respectively (p=0.02). However, even with downtime >20 minutes, 22.9% had a good

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neurologic outcome, and this percentage increased to 37.5% in patients with an initial shockable rhythm.

Conclusions—Although longer downtime is associated with worse outcome in OHCA patients, we found that comatose patients who have been successfully resuscitated and treated with TH have neurologically intact survival rates of 23% even with downtime > 20 minutes.

Keywords

Out-of-Hospital Cardiac Arrest; Therapeutic Hypothermia

1. Introduction

In the past decade, two randomized trials, three meta-analyses, and two registry-based analyses have shown that mild therapeutic hypothermia (TH) (32-34°C for 12-24 hr) in comatose survivors of cardiac arrest reduces mortality and improves neurologic outcome.[1-7] As a result of these studies, the European Resuscitation Council and the American Heart Association recommend mild TH for comatose adult patients with return of spontaneous circulation (ROSC) after out-of-hospital shockable cardiac arrest [ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT)].[8,9,]

Animal models have shown that longer no-flow times are associated with worse neurologic outcome.[10,11] However, early cardiopulmonary resuscitation (CPR) may provide sufficient cerebral circulation to allow for neurologic recovery.[12] Prior clinical reports have shown that prolonged duration of resuscitation efforts in cardiac arrest is associated with poor neurologic outcome.[13-17] However, there are few data addressing this question since the emergence of TH as a standard treatment for comatose patients after cardiac arrest. Clinicians may be reluctant to start TH when ROSC occurs after a prolonged resuscitation effort, in view of the commonly held belief that poor outcome occurs in this context. Longer downtime may even be considered a relative contraindication for TH in some protocols, though there is no clear evidence regarding stratification based on this parameter.[18] This lack of clarity and variation in practice is in part a consequence of the lack of previous investigations addressing the probability of survival after longer downtimes particularly in the era of hypothermia.

The objectives of this study were 1) to determine the relationship between downtime and neurologically intact survival in comatose adult out-of-hospital cardiac arrest (OHCA) patients treated by TH, and 2) to evaluate the rates of survival at prolonged downtimes.

2. Methods

Study design and population

This prospective observational pilot study was conducted between January 2008 and September 2012 at an urban tertiary care teaching hospital, which is a cardiac arrest center, with 650 inpatient beds, and approximately 50,000 Emergency Department (ED) visits per year. The study population consisted of all adult (age > 18 years) OHCA patients with sustained ROSC who were comatose and treated with comprehensive post-arrest care including TH. The institutional indications for TH include adult patients experiencing OHCA (including both shockable and non-shockable initial rhythm), achieving ROSC in the field or in the ED, and presenting in a comatose state (defined as a lack of ability to follow commands) after resuscitation. Patients with life-threatening bleeding were excluded from the institutional hypothermia protocol and patients with profound shock typically were cooled after hemodynamic instability was stabilized on a steady fluid/vasopressor regimen. Exclusion criteria for the current study included traumatic cardiac arrest and patients with unknown duration of downtime in the pre-hospital setting. The hospital Institutional Review Board approved the study.

Data Collection and Patient Management

All patients who presented with OHCA were screened by trained research assistants via the hospital's electronic medical record system. Patient demographic information including age, sex, race, and past medical history were recorded at the time of enrollment. Specific data collected regarding the arrest characteristics included the location of the arrest, total low-flow and no-flow times, whether or not the arrest was witnessed, and whether or not bystander CPR was performed. Vital signs and laboratory data including complete blood count, electrolytes, and lactate were recorded at the time of enrollment. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was also calculated at 24 hours as a severity of illness marker.[19]

Definitions

We defined no-flow time as the time from recognition of cardiac arrest to the start of CPR. In witnessed arrest, time of arrest was defined as time of collapse and in unwitnessed arrest, it was defined as the time that EMS was called. Low-flow time was defined as the time between the start of CPR (by a bystander or EMS) and the time of sustained ROSC. We defined downtime as the time from the recognition of cardiac arrest to the time of sustained ROSC, or no-flow time plus low-flow time. Sustained ROSC was defined as the restoration of a palpable pulse for at least 20 minutes. If ROSC occurred for less than 20 minutes, that time period with a pulse was subtracted from the total downtime calculation if sustained ROSC was subsequently obtained. We defined prolonged downtime as duration of downtime greater than 20 minutes by consensus of the investigators. The primary endpoint was good neurologic outcome. We classified the neurologic status of patients who survived to discharge on the basis of cerebral performance category (CPC) measured at the time of hospital discharge.[20] CPC scores are 1 (no significant impairment), 2 (moderate impairment but able to complete activities of daily living), 3 (severe impairment but conscious), 4 (vegetative state or coma) and 5 (death). Good neurologic outcome was defined as a CPC score of 1 (no major disability) or 2 (moderate disability).

Statistical analysis

Continuous variables are expressed as means with standard deviations, or medians and interquartile range (IQR) if the assumption of a normal distribution was violated. Categorical variables are expressed as numbers and percentages. Demographic and clinical characteristics across the strata of downtime duration (≤10, 11-20, 21-30, >30 min) were assessed using one-way ANOVA or Kruskal-Wallis, Chi-squared or Fisher's exact test, as appropriate. Univariate and multivariate analyses were performed using logistic regression to evaluate the association between downtime and neurologic outcome. The results of multivariate logistic regression are reported as odds ratios (OR) and 95% confidence intervals (CI). A two-sided p value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

During the study period, a total of 174 adult OHCA patients had successful ROSC. Of these, 113 patients were treated with TH. We excluded 8 patients with traumatic arrest and 19 patients who had unknown pre-hospital arrest duration or an undocumented initial rhythm, leaving a total of 86 patients for analysis. The median age was 64.5 (IQR 52.8–76.0) years and 66.3% were male. The median downtime was 18.5 (IQR 10.0–32.3) minutes. Thirty-three patients (38.0%) had a good neurologic outcome, defined as a CPC score of 1 or 2. When downtime was stratified into four groups (≤ 10 min, 11-20 min, 21-30 min, > 30 min), good neurologic outcome rates were 62.5%, 37%, 25%, and 21.7%, respectively (p=0.02). Other baseline characteristics, stratified by duration of downtime are described in Table 1.

We found that downtime [12.0 (7.0-22.0) vs. 23.0 (15.0-38.5), p<0.01], lactate (5.2 ± 2.8 vs. 7.2 ± 3.5, p=0.02), and APACHEII score (22.6 ± 6.1 vs. 27.4 ± 5.8, p=0.01) were significantly different in good neurologic outcome and bad neurologic outcome groups. However, downtime was the only one of these variables that was an independent predictor of decreased chance of good neurologic outcome [OR 1.04 (CI 1.01-1.07), p=0.01] after multivariate analysis.

We then evaluated the rate of good neurologic outcome based on downtime, stratified by initial rhythm. Good neurologic outcome in non-shockable patients was significantly less likely with longer downtime (p=0.01), whereas good neurologic outcomes did not differ significantly in those with initial shockable rhythms (p=0.58) (Figure 1). Among non-shockable patients, only 10.3% (3/29) survived with a good neurologic outcome after a downtime greater than 10 minutes, compared to 61.5% (8/13) in those with a downtime less than 10 minutes. We then examined outcomes in only those patients with prolonged downtime. Patients with downtime > 20 minutes had a neurologically intact survival rate of 22.9% and this percentage increased to 37.5% when looking only at patients with an initial shockable rhythm. Baseline characteristics of this subgroup (downtime > 20 minutes, n=35) were then analyzed to find factors associated with favorable neurologic outcome. In this group, we found that patients with good neurologic outcome had lower lactate levels following ROSC than those with poor neurologic outcome (p=0.02) (Table 2). However, no clear distinguishing characteristics were present that allowed differentiation of patients upon initial presentation. Finally, in the population of patients with a shockable rhythm and much longer downtime (> 30 minutes), 40% (4/10) had a neurologically intact survival (Figure 1).

4. Discussion

This study presents an analysis of downtime with respect to the impact on neurologically intact survival. We found that the overall rate of neurologically intact survival in comatose adult OHCA patients treated by TH was 38.0% and good neurologic outcome was significantly associated with downtime. Among patients with downtime >20 minutes, 22.9% had a good neurologic outcome, and this percentage increased to 37.5% in patients with an initial shockable rhythm.

Previous reports have shown that prolonged duration of resuscitation effort in cardiac arrest is more likely to result in unfavorable neurologic outcome.[13-15,17] Laurent et al.[21] identified a longer time interval as a risk factor for hemodynamic instability after ROSC, and Jorgensen[22] demonstrated that cardiac arrest patients requiring CPR for more than 20 minutes rarely survived. However, these studies were done before TH was the standard of care, and thus outcome in patients requiring prolonged resuscitation who are treated with TH remains uncertain. In the present study, when downtime was stratified into four groups (≤ 10 min, 11-20 min, 21-30 min, > 30 min), neurologically intact survival rates gradually decreased (62.5%, 37%, 25%, and 21.7%, respectively, p=0.02) and downtime was an independent predictor of decreased chance of good neurologic outcome. Such results indicate that downtime is a major determinant of recovery with good neurologic outcome even after TH. However, within this context, a substantial number of survivors with good neurological outcome existed even at downtimes > 30 minutes. The capacity to have good neurologic outcome with prolonged downtime in our sample was similar to recent findings from large studies which analyzed data from the American Heart Association's Get With the Guidelines Resuscitation, a prospective multicenter registry of in-hospital cardiac arrest.[23,24] Goldberger and colleagues [23] report that hospitals where the duration of the cardiopulmonary resuscitation effort is longer on average have significantly better survival rates. In another study analyzing data from in-hospital pediatric cardiac arrest, longer CPR duration was independently associated with lower survival. However, 16.2% of survivors received CPR for >35 minutes; of these survivors, 60% had a good neurologic outcome.[24]

Detailed analysis of the effect of downtime stratified by initial rhythm revealed a high frequency of good neurologic outcome in both shockable and non-shockable rhythms when the downtime was less than 10 minutes. However, the frequency of good neurologic outcome appears to drop rapidly in the non-shockable group as compared to the shockable group as the time interval increases (Figure 1). In this dataset, neurologic outcome did not differ significantly by downtime when patients initially had a shockable rhythm. This finding suggests that patients with an initially shockable rhythm have a particularly good chance of neurologically intact survival even after a prolonged cardiac arrest.

As noted, we found that even with prolonged downtime, patients had a reasonable chance of good neurologic recovery. In order to determine whether neurologically intact survivors could be differentiated upon presentation, we evaluated the subgroup of patients with prolonged downtime (> 20 minutes) for factors present on admission that were associated with good neurologic outcome. In this subgroup, patients with good neurologic outcome had slightly lower lactate levels, however no other associations or outcome predictors were found. Specifically, we did not find an association between comorbidities and outcome in this group. Thus, we were not able to find baseline characteristics to identify patients who would ultimately achieve good neurologic outcome in this group.

Our study was limited by relatively small sample size and the observational design. This was also a single-center study, and results may not be generalizable to other settings. Some selection bias may have occurred if individual clinicians opted not to use TH for a patient with a longer down time, although this is not part of the criteria for TH as used at our hospital. Further data are needed to validate these findings. Another potential concern is that our data included non-sustained ROSC. Since we used the Utstein definition of sustained ROSC as a palpable pulse for > 20 minutes, the possibility remains that our downtime calculation was influenced by patients who had return of pulse and then re-arrested prior to achieving sustained ROSC. When this occurred, we excluded the time the patient had a palpable pulse between arrest periods from our downtime calculation. In patients with un-witnessed arrests we designated the no-flow time as zero. This may have led to an underestimation of no-flow and total downtime in some patients. Finally, 11.4% patients receiving TH had early withdrawal of aggressive care. Our standard guideline in the hospital is to wait for 72 hours. However, reasons do emerge that drive clinical teams to withdraw care earlier than that point, which may have influenced our outcome.

5. Conclusion

Although longer downtime is associated with worse outcome in OHCA patients, we found that comatose patients who have been successfully resuscitated and treated with TH have neurologically intact survival rates of 23% even with prolonged downtime (> 20 minutes)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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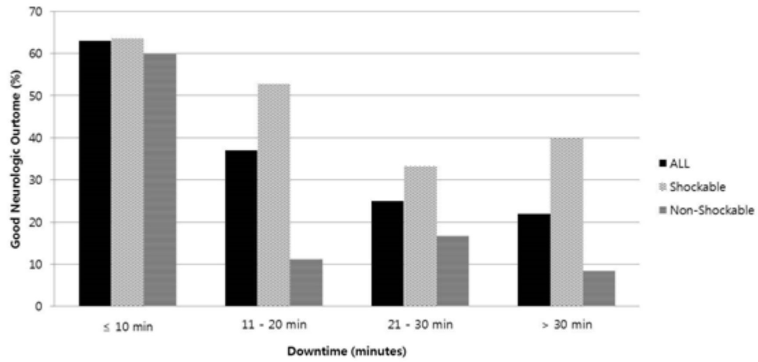

Downtime (minutes)	0 - 10 (n=24)	11 - 20 (n=27)	21 - 30 (n=12)	> 30 (n=23)	p-value
Good CPC(≤2)	15(62.5)	10(37.0)	3(25.0)	5(21.7)	0.02
Non-shockable rhythm (n=42)	8(61.5)	1(10.0)	1(16.7)	1(7.7)	0.01
Shockable rhythm (n=44)	7(63.6)	9(52.9)	2(33.3)	4(40.0)	0.58

Figure 1.

Good neurologic outcome of the out-of-hospital cardiac arrest patients treated with hypothermia, stratified by initial rhythm and duration of downtime

CPC, cerebral performance score, reported as median with interquartile range.

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Table 1

Demographic and baseline characteristics of the out-of-hospital cardiac arrest patients treated with hypothermia, stratified by duration of downtime

	All patients (n=86)	≤ 10 min (n=24)	11 - 20 min (n=27)	21 - 30 min (n=12)	> 30 min (n=23)	p-value
Demographics						
Age, years	64.5(52.8-76.0)	69.5(54.5-77.5)	66.0(54.0-75.0)	69.0(46.0-81.8)	57.0(44.0-72.0)	0.40
Male	57(66.3)	12(50.0)	20(74.1)	8(66.7)	17(73.9)	0.24
Race (white)	69(80.2)	18(75.0)	22(81.5)	9(75.0)	20(87.0)	0.51
Transfer – other hospital	38 (45.8)	9 (37.5)	8 (33.3)	8 (66.7)	13 (56.5)	0.15
Co-morbidities						
Hypertension	41(47.7)	13(54.2)	15(55.6)	6(50.0)	7(30.4)	0.28
Diabetes mellitus	21(24.4)	7(29.2)	9(33.3)	3(25.0)	2(8.7)	0.21
Coronary artery disease	21(24.4)	7(29.2)	10(37.0)	1(8.3)	3(13.0)	0.12
Cancer	3(3.5)	1(4.2)	2(7.4)	0(0.0)	0(0.0)	0.47
No co-morbidities	16(18.6)	4(16.7)	4(14.8)	0(0.0)	8(34.8)	0.07
Arrest characteristics						
Location						0.65
Private/home	36(41.9)	7(29.2)	12(44.4)	5(41.7)	12(52.2)	
Public space	29(33.7)	8(33.3)	12(44.4)	3(25.0)	6(26.1)	
Others or unknown	21(24.4)	9(37.5)	3(11.1)	4(33.3)	5(21.7)	
Witnessed	61(70.9)	21(87.5)	19(70.4)	8(72.7)	13(56.5)	0.13
Bystander CPR	60(69.8)	19(79.2)	20(74.1)	6(50.0)	15(68.2)	0.32
First arrest rhythm						0.51
Shockable	44(51.2)	11(45.8)	17(63.0)	6(50.0)	10(43.5)	
Non-shockable	42(48.8)	13(54.2)	10(37.0)	6(50.0)	13(56.5)	
Low-flow time, min	15.0(8.0-28.8)	6.0(5.0-8.0)	13.5(10.0-15.0)	23.0(17.0-25.0)	40.0(35.0-62.0)	<0.01
Downtime, min	18.5(10.-32.3)	7.0(5.0-10.0)	15.0(13.0-20.0)	25.0(24.3-27.8)	45.0(40.0-65.0)	<0.01
Initial vital signs						
Systolic BP, mmHg	117.5±31.6	128.2±35.3	116.2±29.4	105.5±35.6	115.5±27.0	0.23
Diastolic BP, mmHg	69.7±22.8	81.9±24.4	63.6±18.7	56.8±13.4	70.4±24.0	0.10
Heart rate,/ minute	96.2±26.2	90.5±26.8	104.7±30.3	92.1±22.1	94.3±21.7	0.24
Initial laboratory values						
Lactate, mmol/L	6.6±3.4	4.8±2.2	7.0±3.7	8.2±4.1	7.1±3.1	0.06
Glucose, mg/dL	238.4±116.5	226.5±151.0	255.2±114.3	175.9±51.8	253.0±92.0	0.40
APACHEII score (24 hr)	25.5±6.3	25.0±5.9	26.1±7.9	23.0±5.0	26.8±5.5	0.43

Values are expressed as mean ± SD or median with interquartile range and n (%). CPR, cardiopulmonary resuscitation; BP, blood pressure; WBC, White blood cell count; APACHE II, acute physiology and chronic health evaluation II

Table 2

Demographic characteristics of the prolonged downtime out-of-hospital cardiac arrest patients treated with hypothermia

	All patients (n=35)	Good CPC (≤2) (n=8)	Poor CPC (≥3) (n=27)	p-value
Demographics				
Age, years	60.0(44.0-77.0)	52.5(36.8-74.8)	60.0(53.0-77.0)	0.19
Male	25 (71.4)	6 (75.0)	19 (70.4)	1.00
Race (white)	29 (82.9)	8 (100.0)	21 (77.8)	0.34
Transferred	21 (60.0)	6 (75.0)	15 (55.6)	0.43
Co-morbidities				
Hypertension	13 (37.1)	4 (50.0)	9 (33.3)	0.43
Diabetes mellitus	5 (14.3)	1 (12.5)	4 (14.8)	1.00
Coronary artery disease	4 (11.4)	1 (12.5)	3 (11.1)	1.00
No co-morbidities	8 (22.9)	1 (12.5)	7 (25.9)	0.65
Arrest characteristics				
Location				0.63
Private/home	17 (48.6)	4 (50.0)	13 (48.1)	
Public space	9 (25.7)	3 (37.5)	6 (22.2)	
Others or unknown	9 (25.7)	1 (12.5)	8 (29.6)	
Witnessed	21 (61.8)	4 (57.1)	17 (63.0)	1.00
Bystander CPR	21 (61.8)	4 (57.1)	17 (63.0)	0.68
Shockable rhythm	16 (45.7)	6 (75.0)	10 (37.0)	0.10
Initial vital signs				
Systolic blood pressure, mmHg	111.9 ± 30.1	121.6 ± 28.7	153 ± 33.2	0.53
Diastolic blood pressure, mmHg	66.1 ± 22.0	77.0 ± 22.8	65.9 ± 22.0	0.38
Heart rate, beats per minute	93.5 ± 21.5	92.5 ± 25.2	98.3 ± 26.7	0.50
Initial laboratory values				
Lactate, mmol/L	7.2 ± 3.5	5.2 ± 2.8	7.4 ± 3.4	0.02
Sodium, mmol/L	140.3 ± 3.9	138.8 ± 3.2	140.1 ± 3.4	0.89
Potassium, mmol/L	4.5 ± 1.0	4.1 ± 0.9	4.6 ± 1.1	0.38
Glucose, mmol/L	12.9 ± 5.0	12.2 ± 5.1	13.9 ± 7.2	0.76
APACHEII score (24 hr)	25.5 ± 5.5	22.7 ± 6.0	26.4 ± 5.1	0.13

Values are expressed as mean ± SD and n (%). Statistical analysis was performed by Mann-Whitney U test or Fisher's s exact test.

CPR, cardiopulmonary resuscitation; WBC, White blood cell count; APACHE II, acute physiology and chronic health evaluation II