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Long-Term Prognostic Value of Gasping During Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND Gasping is a natural reflex that enhances oxygenation and circulation during cardiopulmonary resuscitation (CPR).

OBJECTIVES This study sought to assess the relationship between gasping during out-of-hospital cardiac arrest and 1-year survival with favorable neurological outcomes.

METHODS The authors prospectively collected incidence of gasping on all evaluable subjects in a multicenter, randomized, controlled, National Institutes of Health–funded out-of-hospital cardiac arrest clinical trial from August 2007 to July 2009. The association between gasping and 1-year survival with favorable neurological function, defined as a Cerebral Performance Category (CPC) score ≤2 was estimated using multivariable logistic regression.

RESULTS The rates of 1-year survival with a CPC score of ≤2 were 5.4% (98 of 1,827) overall, and 20% (36 of 177) and 3.7% (61 of 1,643) for individuals with and without spontaneous gasping or agonal respiration during CPR, respectively. In multivariable analysis, 1-year survival with CPC ≤2 was independently associated with younger age (odds ratio [OR] for 1 SD increment 0.57; 95% confidence interval [CI]: 0.43 to 0.76), gasping during CPR (OR: 3.94; 95% CI: 2.09 to 7.44), shockable initial recorded rhythm (OR: 16.50; 95% CI: 7.40 to 36.81), shorter CPR duration (OR: 0.31; 95% CI: 0.19 to 0.51), lower epinephrine dosage (OR: 0.47; 95% CI: 0.25 to 0.87), and pulmonary edema (OR: 3.41; 95% CI: 1.53 to 7.60). Gasping combined with a shockable initial recorded rhythm had a 57-fold higher OR (95% CI: 23.49 to 136.92) of 1-year survival with CPC ≤2 versus no gasping and no shockable rhythm.

CONCLUSIONS Gasping during CPR was independently associated with increased 1-year survival with CPC ≤2, regardless of the first recorded rhythm. These findings underscore the importance of not terminating resuscitation prematurely in gasping patients and the need to routinely recognize, monitor, and record data on gasping in all future cardiac arrest trials and registries. (J Am Coll Cardiol 2017;70:1467–76) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CPC = Cerebral Performance Category

CPR = cardiopulmonary resuscitation

EMS = emergency medical service

LOC = level of consciousness

OHCA = out-of-hospital cardiac arrest(s)

OR = odds ratio

ROSC = return of spontaneous circulation

VF = ventricular fibrillation

VT = ventricular tachycardia

Gasping or agonal respirations are relatively common after cardiac arrest, and are associated with increased survival to discharge for out-of-hospital cardiac arrests (OHCA) (1,2). Gasping in the early stage of the arrest may appear to be similar to normal breathing and can contribute to bystanders' or emergency medical dispatchers' delay in recognizing cardiac arrest (3–5).

Though often under-recognized or misinterpreted, the gasping reflex itself is as fundamental to life as breathing. Gasping results in numerous physiological effects, including respiratory gas exchange, decreased right atrial pressure, enhanced cardiac preload, decreased intracranial pressure, and increased aortic, coronary, and cerebral perfusion pressures. As such, gasping enhances respiration and circulation (6,7). Initiation of gasping after cardiac arrest has been linked to the level of brainstem pO_2, arterial baroreceptor and chemoreceptor stimulation following a sudden decrease in blood pressure, and arterial acid-base balance (8). Conversely, restoration of a threshold level of blood flow to the brainstem during cardiopulmonary resuscitation (CPR) has been shown to enhance the gasping reflex (8–10).

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Insufficient knowledge of the long-term importance of gasping during CPR may contribute to the lack of recording, tracking, and attention to this natural biomarker in the setting of cardiac arrest. At present, data are lacking on the potential association between gasping and long-term functional recovery after cardiac arrest. In addition, the potential prognostic value of combining the presence of gasping and the presence of an initial shockable rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT), 2 natural biomarkers predictive of a favorable outcome after cardiac arrest, remains unknown. The primary aim of this study was to examine whether gasping was independently associated with 1-year survival with favorable neurological function. The secondary aim was to determine the potential long-term prognostic value of combining 2 natural biomarkers, gasping and VF/VT.

METHODS

STUDY DESIGN. Prospectively gathered data from a multicenter, randomized, controlled, National Institutes of Health-funded clinical trial that compared standard CPR versus the combination of active compression decompression CPR plus an impedance threshold device for patients in cardiac arrest in subjects with OHCA were used for these analyses (11,12). Data related to increased level of consciousness (LOC) and the presence of gasping were gathered prospectively and analyzed in this observational study, which included all evaluable subjects in the run-in and pivotal phases of the clinical trial from August 2007 to July 2009. The study methodology and the processes that were followed for exception for informed consent have been previously described in detail (11,12).

SUBJECT SELECTION. Subjects included in the present analysis had presumed nontraumatic OHCA of cardiac and noncardiac etiologies. Although noncardiac etiologies were excluded from the primary analysis (11), our analytical study sample included all subjects with the following conditions: cardiac arrest of noncardiac origin (respiratory cause, nontraumatic hemorrhage, stroke, metabolic abnormality, drug overdose, electrocution, or other noncardiac causes), CPR by emergency medical service (EMS) personnel provided for <1 min; complete airway obstruction that could not be cleared or attempts at advanced airway management that were unsuccessful; intubation with a leaky or uncuffed advanced airway device; or a stoma, tracheotomy, or tracheostomy (11). Exclusion criteria were age <18 years, pre-existing do not resuscitate orders, evidence of a traumatic arrest, signs of obvious clinical death, in-hospital cardiac arrest, conditions that precluded the use of CPR, or recent history of sternotomy.

RESUSCITATION PROCEDURES AND DATA COLLECTION. All patients included in the present analysis underwent resuscitation procedures as previously reported (11). At each participating site, a clinical research study coordinator collected data according to the Utstein Guidelines using case report forms (13). The

ACCESS trial, and the National Institute of Neurological Disorders and Stroke: Neurological Emergencies Treatment Trials and Strategies to Innovate Emergency Care Clinical Trials. Dr. Lurie is a consultant for ZOLL Medical and Minnesota Resuscitation Solutions; and is the inventor of the Impedance Threshold Device and Active Compression Decompression CPR. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Comparison of Baseline Characteristics, Intermediary Outcomes, and Processes of Care According to Spontaneous Gasping or Breathing During CPR for OHCA Patients*

	Spontaneous Gasping or Breathing During CPR		
	No (n = 1,683)	Yes (n = 197)	Unadjusted Odds Ratio of Gasping (95% CI)†
Male	1,065 (63)	118 (60)	0.87 (0.63-1.19)
Age, yrs	64 ± 17	63 ± 16	0.97 (0.84-1.13)
Cardiac arrest witnessed	875 (52)	153 (78)	3.27 (2.28-4.76)
Bystander CPR provision	717 (43)	79 (40)	0.90 (0.66-1.23)
Initial recorded cardiac arrest rhythm			
Asystole	931 (56)	34 (18)	1.00
VF or pulseless VT	353 (21)	101 (52)	7.83 (5.21-11.78)
Pulseless electrical activity	376 (23)	58 (30)	4.22 (2.72-6.56)
Emergency call to first response time, min	6.8 ± 3.5	6.1 ± 2.5	0.76 (0.63-0.92)
Emergency call to EMS CPR start time, min‡	7.0 ± 3.6	6.3 ± 2.8	0.76 (0.61-0.94)
Emergency call to placement of study devices, min‡§	7.5 ± 3.6	7.0 ± 3.4	0.86 (0.67-1.10)
Advanced airway during EMS CPR (endotracheal intubation or supraglottic airway)	1,462 (87)	161 (82)	0.66 (0.45-1.01)
Epinephrine dosage, mg	3.4 ± 2.2	2.6 ± 2.6	0.70 (0.60-0.83)
Duration of CPR, min	27 ± 12	23 ± 14	0.72 (0.62-0.83)
ROSC during pre-hospital CPR	631 (38)	150 (76)	5.32 (3.74-7.65)
Elevated level of conscience during prehospital CPR	21 (1.3)	43 (22)	22.08 (12.41-40.10)
Pulmonary edema	148 (8.8)	26 (13)	1.58 (0.97-2.49)
Admitted to hospital	436 (26)	114 (58)	3.93 (2.87-5.39)
In-hospital procedures‖			
Induced hypothermia	160/436 (37)	48/114 (42)	1.25 (0.80-1.95)
Cardiac catheterization	95/436 (22)	51/114 (45)	2.91 (1.84-4.58)
Coronary stenting	31/436 (7.1)	15/114 (13)	1.98 (0.95-3.95)
Coronary bypass surgery	7/436 (1.6)	6/114 (5.3)	3.40 (0.92-12.07)
Implanted cardioverter-defibrillator	29/436 (6.7)	28/114 (25)	4.57 (2.47-8.38)
Survival to hospital discharge	132 (7.9)	67 (34)	6.07 (4.22-8.67)
CPC score ≤2 at hospital discharge	80 (4.8)	51 (26)	7.09 (4.69-10.64)
MRS score ≤3 at hospital discharge	80 (4.8)	48 (25)	6.54 (4.29-9.87)

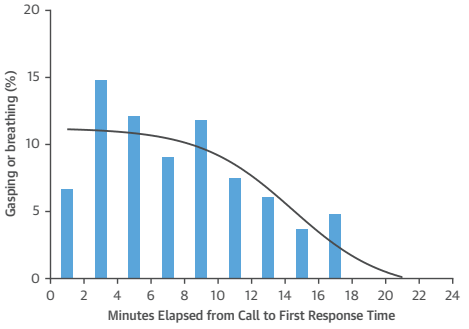
Values are n (%), mean ± SD, or n/N (%), unless otherwise indicated. *The analytical sample consisted of 1,888 patients. Values were missing for spontaneous gasping or breathing during CPR (n = 8), age (n = 2), cardiac arrest surroundings (n = 6), bystander CPR (n = 2), initial recorded cardiac arrest rhythm (n = 28), emergency call to first response time (n = 1), emergency call to EMS CPR start time (n = 2), emergency call to placement of study devices (n = 26), advanced airway during EMS CPR (n = 4), elevated level of conscience (n = 8), ROSC during prehospital CPR (n = 2), duration of CPR (n = 1), survival to hospital discharge (n = 9), CPC (n = 15), and MRS (n = 14) scores at hospital discharge. †Odds ratios were expressed for 1 SD increment in patient age, emergency call to first response time, emergency call to EMS CPR start time, emergency call to placement of study devices, duration of CPR and epinephrine dosage. ‡Data did not include cardiac arrests witnessed by EMS personnel. §Data included active compression-decompression cardiopulmonary resuscitation recipients only. ‖Data included patients admitted to hospital only.

CI = confidence interval; CPC = cerebral performance category; CPR = cardiopulmonary resuscitation; EMS = emergency medical services; MRS = modified Rankin scale; OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; VF = ventricular fibrillation; VT = ventricular tachycardia.

information entered onto the case report forms came from multiple sources, including the EMS run reports for all patients, a "study hotline" call that was made within hours after the cardiac arrest by the medic-in-charge of the arrest to an on-call research team, interviews made within 1 to 2 days after the cardiac arrest by the study site research coordinator and the EMS crews at the scene of the arrest, hospital records, and neurological assessment surveys for all patients that gave consent. Pulmonary edema was defined as fluid present in the advanced airway or in the impedance threshold device or diagnosis of pulmonary edema on first x-ray or computed tomography scan.

In the first year of the study, it was observed that some subjects had agonal respirations or showed other signs of awakening, such as biting on the

FIGURE 1 Prevalence of Spontaneous Gasping or Breathing According to Call to First Response Time



The analytical sample consisted of 1,888 patients. Values are missing for spontaneous gasping or breathing during CPR (n = 8) and emergency call to first response time (n = 1). CPR = cardiopulmonary resuscitation.

TABLE 2 Comparison of 1-Yr Survival With CPC ≤2 According to Baseline Characteristics, Intermediary Outcomes, and Processes of Care for OHCA Patients*

	N	1-Yr Survivors With CPC ≤2	Unadjusted Odds Ratio of 1-Yr Survival With CPC ≤2 (95% CI)
Sex			
Female	671	31 (4.6)	1.00
Male	1,156	67 (5.8)	1.27 (0.81–2.04)
Age, yrs			
18–35	100	7 (7.0)	1.00
35–45	133	11 (8.3)	1.20 (0.45–3.21)
45–55	288	20 (6.9)	0.99 (0.41–2.42)
55–65	383	25 (6.5)	0.93 (0.39–2.21)
65–75	350	23 (6.6)	0.93 (0.39–2.24)
75–85	347	7 (2.0)	0.27 (0.09–0.80)
≥85	224	5 (2.2)	0.30 (0.09–0.98)
Cardiac arrest witnessed			
Unwitnessed	837	18 (2.2)	1.00
Bystander/EMS witnessed	984	80 (8.1)	4.03 (2.37–7.19)
Bystander CPR provision			
No	1,050	60 (5.7)	1.00
Yes	775	38 (4.9)	0.85 (0.54–1.31)
Initial recorded cardiac arrest rhythm			
Asystole	958	9 (0.9)	1.00
VF or pulseless VT	422	75 (18)	22.79 (11.29–46.00)
Pulseless electrical activity	426	10 (2.4)	2.53 (1.02–6.28)
Emergency call to first response time, min			
0–5	374	41 (11)	1.00
≥5	1,452	57 (3.9)	0.33 (0.21–0.52)
Emergency call to EMS CPR start time, min†			
0–5	293	29 (9.9)	1.00
≥5	1,316	45 (3.4)	0.37 (0.23–0.59)
Emergency call to placement of study devices, min†‡			
0–5	124	15 (12)	1.00
≥5	685	23 (3.4)	0.25 (0.12–0.54)
Advanced airway during EMS CPR			
No	234	29 (12)	1.00
Yes	1,589	69 (4.3)	0.32 (0.20–0.53)
Epinephrine use			
No	226	56 (25)	1.00
Yes	1,601	42 (2.6)	0.09 (0.04–0.18)
Duration of CPR, min			
0–15	332	71 (21)	1.00
≥15	1,494	27 (1.8)	0.07 (0.04–0.11)
ROSC during pre-hospital CPR			
No	1,100	4 (0.4)	1.00
Yes	725	94 (13)	40.82 (15.29–153.41)
Spontaneous gasping or breathing during CPR			
No	1,643	61 (3.7)	1.00
Yes	177	36 (20)	6.62 (4.10–10.55)
Elevated level of conscience			
No	1,766	81 (4.6)	1.00
Yes	54	17 (31)	9.56 (4.82–18.23)
Pulmonary edema			
No	1,663	80 (4.8)	1.00
Yes	164	18 (11)	2.44 (1.34–4.24)
Admitted to hospital			
No	1,333	0 (0.0)	1.00
Yes	494	98 (20)	–

Continued on the next page

TABLE 2 Continued

	N	1-Yr Survivors With CPC ≤2	Unadjusted Odds Ratio of 1-Yr Survival With CPC ≤2 (95% CI)
Induced hypothermia§			
No	300	46 (15)	1.00
Yes	194	52 (27)	2.02 (1.26–3.24)
Cardiac catheterization§			
No	370	20 (5.4)	1.00
Yes	124	78 (63)	29.67 (16.07–55.60)
Coronary stenting§			
No	454	72 (16)	1.00
Yes	40	26 (65)	9.85 (4.67–21.32)
Coronary bypass surgery§			
No	483	87 (18)	1.00
Yes	11	11 (100)	–
Implanted cardioverter-defibrillator§			
No	447	52 (12)	1.00
Yes	47	46 (98)	–

Values are n (%) unless otherwise indicated. *The analytical sample consisted of 1,827 patients with documented 1-year survival and cerebral performance category score. Values were missing for age (n = 2), cardiac arrest surroundings (n = 6), bystander CPR (n = 2), initial recorded cardiac arrest rhythm (n = 21), emergency call to first response time (n = 1), emergency call to EMS CPR start time (n = 2), emergency call to placement of study devices (n = 25), advanced airway during EMS CPR (n = 4), spontaneous gasping or breathing during CPR (n = 7), elevated level of conscience (n = 7), ROSC during prehospital CPR (n = 2), and duration of CPR (n = 1). †Data did not include cardiac arrests witnessed by EMS personnel. ‡Data included active compression-decompression cardiopulmonary resuscitation recipients only. §Data included patients admitted to hospital only.

Abbreviations as in Table 1.

endotracheal tube, unanticipated arm movements, eye movement, mumbling, talking during CPR, and the like. The study case report form was modified in October 2006 to query, "Did EMS personnel report signs/symptoms of an elevated LOC during the performance of CPR?" and during the call-in report that followed each arrest, EMS personnel were asked, "Did you notice any signs/symptoms of an elevated LOC during the performance of CPR, such as gagging, gasping, eye opening or other body movement?" Beginning in August 2007, the case report forms were further modified to query specifically about gasping as follows: "Did the subject gasp or breathe (at any rate) during the performance of CPR?" The call-in report also focused on the same question to include whether or not gasping was observed at any time during the arrest and the duration of the gasping. Review of all case report forms revealed that 1,880 of 1,888 subjects (99.6%) had the gasping data field completed on the case report form.

OUTCOME MEASURES. The primary endpoint for the present analysis was 1-year survival with favorable neurological function, defined as a Cerebral Performance Category (CPC) score of 1 or 2. A CPC score ≤2 was prospectively determined to be indicative of favorable neurological function.

STATISTICAL ANALYSIS. Baseline characteristics were reported as number and percentage for categorical variables and mean and SD for continuous variables. We compared baseline characteristics for subjects with versus without spontaneous gasping or breathing during pre-hospital CPR. With univariable analyses, we estimated unadjusted odds ratios (ORs) of 1-year survival with favorable neurological function along with 95% confidence intervals (CIs) for baseline characteristics. With multivariable analyses, we performed logistic regression to examine the independent association between spontaneous gasping or breathing during pre-hospital CPR and 1-year survival with favorable neurological function. ORs were adjusted for study intervention arm, pre-specified prognostic factors (e.g., age, sex, cardiac arrest witnessed, bystander CPR provision, initial recorded cardiac arrest rhythm, time from emergency call to first response time, total CPR duration, pulmonary edema, and epinephrine dosage), and study sites. To assess the robustness of our findings, we stratified multivariable analysis according to VF or pulseless VT on the first recorded cardiac rhythm. We also examined whether the relationship between spontaneous gasping and 1-year survival with favorable neurological function remained significant after restricting the study sample to individuals who experienced return of spontaneous circulation (ROSC) during the performance of pre-hospital CPR.

We performed multiple imputations of missing values for covariates. Fifty imputed datasets were created with a total run length of 50,000 iterations and imputations made every 1,000 iterations. For the

purpose of analysis, 2 independent variables (i.e., gasping and first recorded cardiac rhythm) were combined into a single polytomous variable, with the categories indicating no gasping with no VF/VT (reference), no gasping with VF/VT, gasping with no VF/VT, and gasping with VF/VT, respectively. Two-sided p values < 0.05 were considered statistically significant. All analyses were performed using Stata version 14.0 Special Edition (Stata Corporation, College Station, Texas).

RESULTS

From August 2007 to July 2009, 1,888 subjects with OHCA were recruited, including 1,880 for whom information on spontaneous gasping or breathing was recorded, 1,840 with documented 1-year survival, and 1,827 with documented CPC score at 1 year. The mean age for all 1,888 subjects was 64 ± 17 years, 1,189 (63%) were male, 799 (42%) were provided CPR by bystanders, and 456 (24%) had a first recorded shockable initial cardiac rhythm of VF/VT.

Overall, 197 subjects (10%) were documented to have spontaneous gasping or agonal respirations before or during CPR. Subjects with spontaneous gasping or agonal respirations had higher odds of also having a witnessed cardiac arrest, an initial cardiac rhythm of VF/VT, or pulseless electrical activity, ROSC, and an elevated LOC during pre-hospital CPR (Table 1). Conversely, subjects with agonal respirations experienced shorter first response and EMS CPR start times (Figure 1). They were also more likely to receive shorter pre-hospital CPR duration and lower epinephrine dosage, to be admitted to hospital, and to undergo in-hospital cardiac catheterization and implanted cardioverter-defibrillator procedures. Spontaneous gasping was reported for 47 (4.3%) of 1,098 individuals without ROSC. The rate of bystander CPR did not differ according to the incidence of agonal respirations (Table 1).

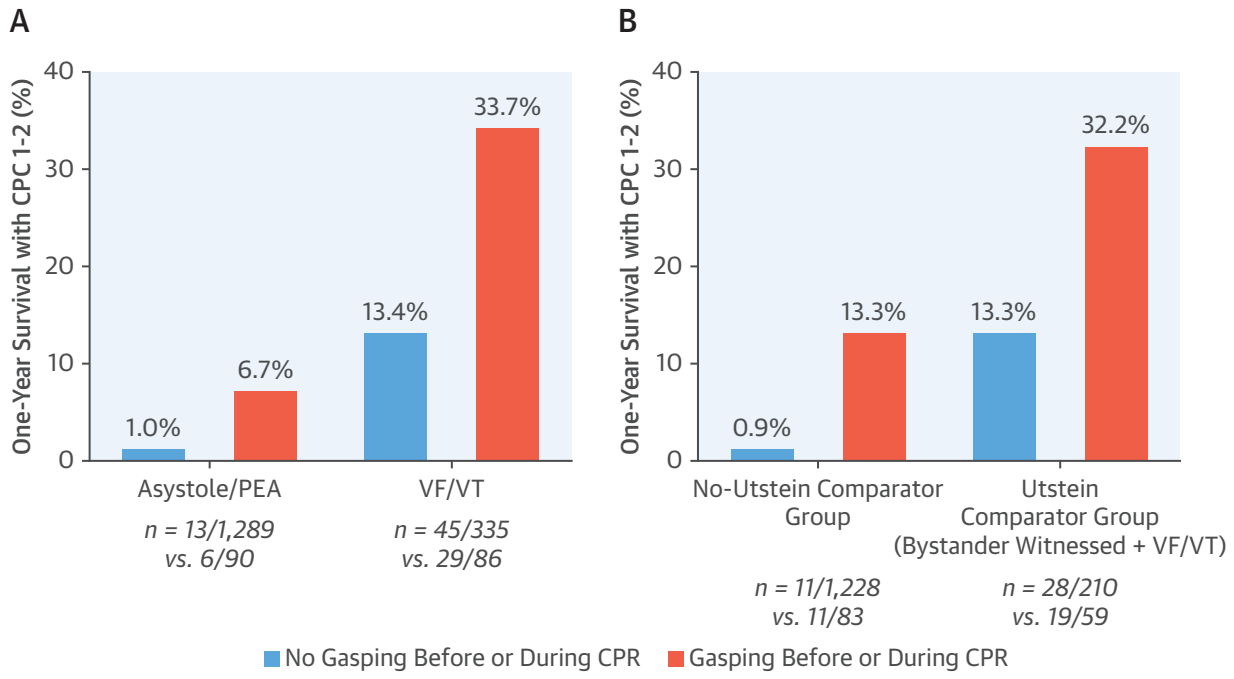
The 1-year survival and 1-year survival with CPC ≤2 rates in the study population were 6.4% (118 of 1,840) and 5.4% (98 of 1,827), respectively. The rates of 1-year survival with a CPC score of ≤2 were 20% (36 of 177) and 3.7% (61 of 1,643) for individuals with and without spontaneous gasping or agonal respiration during CPR (OR: 6.62; 95% CI: 4.10 to 10.55). Other characteristics associated with higher odds of 1-year survival with CPC ≤2 in univariable analysis included an initial rhythm of VF/VT or pulseless electrical activity, witnessed arrest, elevated LOC, pulmonary edema, and pre-hospital ROSC (Table 2). Conversely, 1-year survivors with CPC ≤2 were younger, experienced shorter first response and EMS CPR start times, and CPR duration, and were less likely to receive epinephrine and to undergo placement of an advanced airway (Table 2). Furthermore, the occurrence of gasping was highly associated with improved long-term survival with favorable brain function, whether the first recorded cardiac rhythm was VF/VT or pulseless electrical activity/asystole (Central Illustration). The same improved outcome was observed within Utstein comparator group (bystander witnessed arrest and VF/VT) or no-Utstein comparator group (Central Illustration).

In multivariable analysis, 1-year survival with a CPC ≤2 remained independently associated with gasping, pulmonary edema, and a shockable initial cardiac rhythm after adjusting for baseline characteristics (Table 3). The odds of survival with favorable neurological outcome associated with gasping did not vary according to initial recorded cardiac rhythm (p for interaction = 0.52) (Table 4). After restricting the study sample to 725 individuals who experienced ROSC during pre-hospital CPR, spontaneous gasping or agonal respirations still remained independently associated with 1-year survival with CPC ≤2 in multivariable analysis (adjusted OR: 2.31; 95% CI: 1.19 to 4.51).

DISCUSSION

The study results demonstrate that during CPR the occurrence of spontaneous gasping, a natural biomarker for the presence of brainstem activity, was independently associated with a 3.9-fold higher odds of long-term survival with good brain function. To our knowledge, this study is the first to report a relationship between long-term survival with favorable neurological function after OHCA and gasping or agonal breathing before or during CPR. Regardless of the presenting rhythm, 37% of survivors with favorable brain function had agonal respirations during CPR. Moreover, gasping was more highly associated with 1-year survival with good brain function than any predictive variable other than VF/VT as the first recorded rhythm. The combination of gasping or agonal respirations and VF/VT as the first recorded rhythm was associated with remarkable 57-fold higher odds of 1-year survival with good brain function compared with no gasping and no VF/VT. These new findings underscore the importance and clinical significance of recognizing gasping during CPR and recording the presence of gasping on run-reports, during clinical trials, and in CPR registries. From a clinical perspective, the new results provide a potential rationale for not terminating CPR prematurely in patients with ongoing gasping efforts. The new

CENTRAL ILLUSTRATION **Gasping and Neurologic Outcome After OHCA**



Debaty, G. et al. J Am Coll Cardiol. 2017;70(12):1467-76.

(A) The n (%) of 1-year survivors with CPC ≤2 stratified by spontaneous gasping or breathing during CPR and initial recorded cardiac arrest rhythm. The crude odds ratios of 1-year survival with CPC ≤2 associated with spontaneous gasping or breathing during CPR were 3.28 (95% confidence interval [CI]: 1.82 to 5.84) and 7.01 (95% CI: 2.12 to 20.35) for subjects with and without shockable cardiac rhythm, respectively (p for interaction = 0.18). **(B)** The n (%) of 1-year survivors with CPC ≤2 stratified by spontaneous gasping or breathing during CPR and Utstein comparator group. The crude odds ratios of 1-year survival with CPC ≤2 associated with spontaneous gasping or breathing during CPR were 3.09 (95% CI: 1.47 to 6.37) and 16.90 (95% CI: 6.37 to 44.34) for Utstein style comparator and control groups, respectively (p for interaction = 0.002). The analytical sample consisted of 1,661 patients after excluding 227 cardiac arrests witnessed by emergency medical services. Values were missing for spontaneous gasping or breathing during CPR (n = 8), initial recorded cardiac arrest rhythm (n = 21), cardiac arrest surroundings (n = 6), and 1-year survival with CPC score (n = 50). CI = confidence interval; CPC = cerebral performance category; CPR = cardiopulmonary resuscitation; OHCA = out-of-hospital cardiac arrest; PEA = pulseless electrical activity; VF = ventricular fibrillation; VT = ventricular tachycardia.

findings also lead us to question whether it may be harmful to suppress gasping pharmacologically during CPR.

The presence of gasping or agonal breathing has been previously reported to be as high as 30% to 40% in the first minutes after cardiac arrest. The gasping frequency has been reported to decrease over time such that only 7% of patients have been reported to gasp when EMS arrival was >9 min after arrest (1,3,14,15). Consistent with these prior studies, the mean time from emergency call for help to arrival to the patient was 6.7 ± 3.4 min with a 10% prevalence of gasping recorded prospectively in the present study.

It has been previously observed that gasping or agonal breathing can increase the difficulty a bystander has recognizing cardiac arrest. Therefore, a special focus on whether a patient is gasping is recommended during CPR classes as well as for dispatchers during call-taking and the dispensing of pre-arrival instructions and dispatcher-assisted CPR (4,5,16–21). In resuscitation studies using standard CPR in a porcine model of cardiac arrest, gasping was more likely to continue or, when absent, start with shorter untreated VF duration or the use of continuous high-quality chest compressions (9). In a meta-analysis totaling 10,797 participants, gasping was associated with an increased relative risk of survival to hospital discharge (3.53; 95% CI: 3.03 to 4.10) (1). Our study extends this previous finding, with long-term survival with good brain function estimates being consistent in magnitude.

Our findings are in accordance with published reports on the association between survival with good

TABLE 3 Independent Association of Spontaneous Gasping or Breathing During CPR With 1-Yr Survival With CPC ≤2 for Out-of-Hospital Cardiac Arrest Patients (n = 1,827)*

	Adjusted Odds Ratio (95% CI)†
Spontaneous gasping or breathing during CPR	3.94 (2.09–7.44)
Male	1.49 (0.83–2.68)
Age, yrs	0.57 (0.43–0.76)
Pulmonary edema	3.41 (1.53–7.60)
Cardiac arrest witnessed	1.49 (0.76–2.92)
Bystander CPR provision	1.19 (0.68–2.08)
Initial recorded cardiac arrest rhythm, min	
Asystole	1.00
VF or pulseless VT	16.50 (7.40–36.81)
Pulseless electrical activity	1.22 (0.45–3.34)
Emergency call to first response time, min	0.75 (0.51–1.09)
Total CPR duration, min	0.31 (0.19–0.51)
Epinephrine dosage, mg	0.47 (0.25–0.87)

*The analytical sample consisted of 1,827 patients with documented 1-yr survival and cerebral performance category score, after multiple imputation of missing values for 34 patients with a missing value for 1 or more covariates (age [n = 2], cardiac arrest surroundings [n = 6], bystander CPR [n = 2], initial recorded cardiac arrest rhythm [n = 21], emergency call to first response time [n = 1], spontaneous gasping or breathing at any time during CPR [n = 7], elevated level of conscience [n = 7], ROSC during prehospital CPR [n = 2], and duration of CPR [n = 1]). Fifty imputed datasets were created with a total run length of 50,000 iterations and imputations made every 1,000 iterations. †Odds ratios were adjusted for study arm and site. Odds ratios were expressed for 1 SD increment in patient age, emergency call to first response time, total CPR duration, and epinephrine dosage.

Abbreviations as in Table 1.

neurological function and pre-hospital variables, such as VF as the first recorded rhythm, age, and CPR duration. They are also consistent with the multiple beneficial physiological effects of gasping including a transient reduction in intrathoracic pressure and improved cardiopulmonary and cerebral circulation (6,10,15). Further, a significant and independent association was observed between the presence of pulmonary edema and a higher likelihood of survival with good neurological function (11). Our results also highlight a strong negative association between the pre-hospital use of epinephrine and long-term survival with good brain function. As previously reported in observational, registry-based studies, the total dosage of epinephrine is closely linked to 1-year survival with favorable neurological outcome (22–25). In the present analysis, each additional 2-mg increment of epinephrine dosage was associated with a 50% odds of poorer outcome.

At present, there are few biomarkers that can be used to guide resuscitations efforts or predict outcomes. The presence of an initial rhythm of VF/VT has been long recognized as a natural biomarker; when present VF/VT is associated with ≤20 times higher likelihood of survival (26). End-tidal CO_2 levels have also been used as a biomarker to predict circulation and survival (27). The current finding demonstrates that gasping by itself, or combined with the presence of VF/VT, is another important biomarker that should be used routinely to guide resuscitation efforts and prognostication. The current study also demonstrated that the presence of pulmonary edema was independently associated with long-term survival. At present, the underlying mechanisms linking the development of pulmonary edema and improved 1-year survival with favorable neurological outcomes are likely to be multifactorial.

STUDY LIMITATIONS. First, we performed an unplanned secondary analysis using prospectively gathered data from a randomized controlled trial, and

TABLE 4 Independent Association of Spontaneous Gasping or Breathing During CPR With 1-Yr Survival With CPC ≤2 Stratified by Initial Recorded Cardiac Rhythm*

	Ventricular Fibrillation or Pulseless Ventricular Tachycardia†		
	Yes (n = 422)	No (n = 1,384)	p Value for Interaction
Spontaneous gasping or breathing during CPR	3.32 (1.53–7.22)	5.36 (1.61–17.84)	0.52
Age, yrs	0.52 (0.35–0.77)	0.57 (0.36–0.92)	0.63
Male	2.30 (1.05–5.06)	0.61 (0.22–1.65)	0.02
Pulmonary edema	4.68 (1.64–13.37)	0.94 (0.17–5.22)	0.17
Cardiac arrest witnessed	1.40 (0.60–3.30)	2.35 (0.71–7.82)	0.40
Bystander CPR provision	0.90 (0.45–1.81)	3.12 (0.82–11.93)	0.09
Emergency call to first responder CPR start time, min	0.66 (0.40–1.10)	0.89 (0.51–1.55)	0.47
Total CPR duration, min	0.29 (0.15–0.54)	0.34 (0.14–0.82)	0.90
Epinephrine dosage, mg	0.45 (0.21–0.96)	0.48 (0.15–1.52)	0.98

Values are odds ratio (95% confidence interval). *The analytical sample consisted of 1,806 patients with documented 1-yr survival with favorable neurologic outcome, after multiple imputation of missing values for 13 patients with a missing value for 1 or more covariates (age [n = 1], cardiac arrest surroundings [n = 5], bystander CPR [n = 1], elevated level of conscience [n = 5], ROSC during prehospital CPR [n = 1], and spontaneous gasping or breathing at any time during CPR [n = 6]). Fifty imputed datasets were created with a total run length of 50,000 iterations and imputations made every 1,000 iterations. †Odds ratios were adjusted for study arm and site. Odds ratios were expressed for 1 SD increment in patient age, emergency call to first response time, total CPR duration, and epinephrine dosage.

Abbreviations as in Table 1.

the associations are therefore observational in nature. Although, multivariable analysis adjusted for imbalances in baseline characteristics supported the robustness of our findings, we cannot exclude confounding by unmeasured prognostic factors. Second, although information on gasping or breathing before or during CPR was specified in data prospectively collected as part of the trial, we did not record the detail on timing, respiratory patterns, or frequency. Hence, we were not able to investigate the temporal relationship between gasping and ROSC. It is also possible that different respiratory patterns could provide different effects on long-term survival. Of note, we did not observe an increase in gasping when bystander CPR was performed. Third, the presence of gasping was somewhat lower than what others have reported, even though the time from 911 call receipt to first professional responder on scene was a relatively short average of 6.7 min. As such, we may have underestimated the association between gasping and long-term survival with favorable brain function. Finally, it is unknown whether efforts to suppress agonal respirations may be beneficial or harmful during cardiac arrest, but we speculate that based upon these study results, it may not be prudent to suppress gasping during CPR.

CONCLUSIONS

Gasping during CPR was independently associated with a higher likelihood of 1-year survival with favorable neurological status after OHCA. Besides VF/VT as the presenting cardiac rhythm, spontaneous gasping before or during CPR appears to be a natural biomarker and a major prognostic variable in predicting 1-year survival with favorable brain function. The combination of these 2 natural biomarkers, gasping and VF/VT, provides the highest reported predictive markers of long-term survival with favorable brain function. These findings underscore the clinical importance of recognizing gasping during CPR and provide a potential rationale for not terminating chest compressions or inhibiting spontaneous inspiratory efforts in a gasping patient during CPR. On the basis of its clinical and prognostic value, gasping before or during CPR should be prospectively collected in all clinical CPR trials and registries.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Gasping during CPR is a predictor of long-term survival with favorable brain function after out-of-hospital cardiac arrest, regardless of the presenting cardiac rhythm.

TRANSLATIONAL OUTLOOK: Further studies are needed to assess the impact on outcomes of CPR protocols that monitor for and record gasping and consider the presence of gasping in deciding to continue resuscitation efforts.

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